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(54) **QUINOLINES AS FGFR KINASE MODULATORS**

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C07D 401/04	(2006.01)
C07D 407/14	(2006.01)
A61K 31/4709	(2006.01)
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A61K 31/5377	(2006.01)
A61K 45/06	(2006.01)
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See application file for complete search history.

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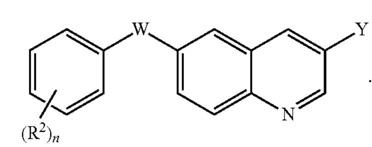
(57) **ABSTRACT**

The invention relates to new quinoline derivative compounds of formula (I), to pharmaceutical compositions comprising said compounds, to processes for the preparation of said compounds and to the use of said compounds in the treatment of diseases, e.g. cancer. Formula (I)

(I)



20 Claims, No Drawings

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QUINOLINES AS FGFR KINASE MODULATORS

CROSS REFERENCE TO RELATED APPLICATIONS

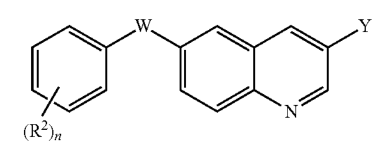
This is a national stage filing under Section 371 of International Application No. PCT/GB2012/052666 filed on Oct. 26, 2012, and published in English as WO 2013/061074 A1 on May 2, 2013, and claims priority to British Application No. 1118652.5 filed on Oct. 28, 2011 and to U.S. Provisional Application No. 61/552,880 filed on Oct. 28, 2011. The entire disclosures of each of the prior applications are hereby incorporated herein by reference.

FIELD OF THE INVENTION

The invention relates to new quinoline derivative compounds, to pharmaceutical compositions comprising said compounds, to processes for the preparation of said compounds and to the use of said compounds in the treatment of diseases, e.g. cancer.

SUMMARY OF THE INVENTION

According to a first aspect of the invention there is provided compounds of formula (I):



(I)

including any tautomeric or stereochemically isomeric form thereof, wherein

W is —N(R^3)— or —C($R^{3a}R^{3b}$)—;

each R^2 is independently selected from hydroxyl, halogen, cyano, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkoxy, hydroxyC_{1-4}alkyl, hydroxyC_{1-4}alkoxy, haloC_{1-4}alkyl, haloC_{1-4}alkoxy, hydroxyhaloC_{1-4}alkyl, hydroxyhalo-C_{1-4}alkoxy, C_{1-4}alkoxyC_{1-4}alkyl, haloC_{1-4}alkoxyC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl wherein each C_{1-4}alkyl may optionally be substituted with one or two hydroxyl groups, hydroxy-haloC_{1-4}alkoxyC_{1-4}alkyl, R^{13}, C_{1-4}alkyl substituted with R^{13}, C_{1-4}alkyl substituted with —C(═O)—R^{13}, C_{1-4}alkoxy substituted with R^{13}, C_{1-4}alkoxy substituted with —C(═O)—R^{13}, —C(═O)—R^{13}, C_{1-4}alkyl substituted with —NR^7R^8, C_{1-4}alkyl substituted with —C(═O)—NR^7R^8, C_{1-4}alkoxy substituted with —NR^7R^8, C_{1-4}alkoxy substituted with —C(═O)—NR^7R^8, —NR^7R^8 and —C(═O)—NR^7R^8; or when two R^2 groups are attached to adjacent carbon atoms they may be taken together to form a radical of formula:

—O—(C(R^{17})$_2$)$_p$—O—;

—X—CH═CH—; or

—X—CH═N—;

wherein R^{17} represents hydrogen or fluorine, p represents 1 or 2 and X represents O or S;

Y represents —CR^{18}═N—OR^{19} or -E-D;

D represents a 3 to 12 ring membered monocyclic or bicyclic carbocyclyl or a 3 to 12 ring membered monocyclic or bicyclic heterocyclyl containing at least one heteroatom selected from N, O or S, wherein said carbocyclyl and heterocyclyl may each be optionally substituted by one or more (e.g. 1, 2 or 3) R^1 groups;

E represents a bond, —($CR^{22}R^{23}$)$_n$—, C_{2-4}alkenediyl optionally substituted with R^{22}, C_{2-4}alkynediyl optionally substituted with R^{22}, —O—($CR^{22}R^{23}$)$_s$—, —($CR^{22}R^{23}$)$_s$—O—, —NR^{22}—($CR^{22}R^{23}$)$_s$—, —($CR^{22}R^{23}$)$_s$—NR^{22}—, —O—($CR^{22}R^{23}$)$_s$—, —($CR^{22}R^{23}$)$_s$—O—, —S(O)$_m$—($CR^{22}R^{23}$)$_s$—, —($CR^{22}R^{23}$)$_s$—S(O)$_m$—, —($CR^{22}R^{23}$)—CO—NR^{22}—($CR^{22}R^{23}$)$_s$— or —($CR^{22}R^{23}$)—NR^{22}—CO—($CR^{22}R^{23}$)$_s$—;

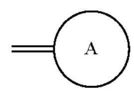
R^1 represents hydrogen, halo, cyano, C_{1-6}alkyl, C_{1-6}alkoxy, —C(═O)—O—C_{1-6}alkyl, C_{2-4}alkenyl, hydroxyC_{1-6}alkyl, haloC_{1-6}alkyl, hydroxyhaloC_{1-6}alkyl, cyanoC_{1-4}alkyl, C_{1-6}alkoxyC_{1-6}alkyl wherein each C_{1-6}alkyl may optionally be substituted with one or two hydroxyl groups, —NR^4R^5, C_{1-6}alkyl substituted with —O—C(═O)—C_{1-6}alkyl, C_{1-6}alkyl substituted with —NR^4R^5, —C(═O)—NR^4R^5, —C(═O)—C_{1-6}alkyl-NR^4R^6, C_{1-6}alkyl substituted with —C(═O)—NR^4R^5, —S(═O)$_2$-haloC_{1-6}alkyl, —S(═O)$_2$—$NR^{14}R^{15}$, substituted with —S(═O)$_2$—C_{1-6}alkyl, C_{1-6}alkyl substituted with —S(═O)$_2$-halo-C_{1-6}alkyl, C_{1-6}alkyl substituted with —S(═O)$_2$—$NR^{14}R^{15}$, C_{1-6}alkyl substituted with —NH—S(═O)$_2$—C_{1-6}alkyl, C_{1-6}alkyl substituted with —NH—S(═O)$_2$-haloC_{1-6}alkyl, C_{1-6}alkyl substituted with —NR^{12}—S(═O)$_2$—$NR^{14}R^{15}$, R^6, C_{1-6}alkyl substituted with R^6, —C(═O)—R^6, C_{1-6}alkyl substituted with —C(═O)—R^6, hydroxyC_{1-6}alkyl substituted with R^6, C_{1-6}alkyl substituted with —Si(CH_3)$_3$, C_{1-6}alkyl substituted with —P(═O)(OH)$_2$ or C_{1-6}alkyl substituted with —P(═O)(OC_{1-6}alkyl)$_2$;

R^{3a} represents —$NR^{10}R^{11}$, hydroxyl, C_{1-6}alkoxy, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxy substituted with —$NR^{10}R^{11}$, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, halo-C_{1-6}alkyl optionally substituted with —O—C(═O)—C_{1-6}alkyl, hydroxyC_{1-6}alkyl optionally substituted with —O—C(═O)—C_{1-6}alkyl hydroxyC_{2-6}alkenyl, hydroxy-C_{2-6}alkynyl, hydroxyhaloC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkyl substituted with carboxyl, C_{1-6}alkyl substituted with —C(═O)—C_{1-6}alkyl, C_{1-6}alkyl substituted with —C(═O)—O—C_{1-6}alkyl, C_{1-6}alkyl substituted with C_{1-6}alkoxyC_{1-6}alkyl-O—C(═O)—, C_{1-6}alkyl substituted with C_{1-6}alkoxyC_{1-6}alkyl-C(═O)—, C_{1-6}alkyl substituted with —O—C(═O)—C_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkyl wherein each C_{1-6}alkyl may optionally be substituted with one or two hydroxyl groups or with —O—C(═O)—C_{1-6}alkyl, C_{2-6}alkenyl substituted with C_{1-6}alkoxy, C_{2-6}alkynyl substituted with C_{1-6}alkoxy, C_{1-6}alkyl substituted with R^9 and optionally substituted with —O—C(═O)—C_{1-6}alkyl, C_{1-6}alkyl substituted with —C(═O)—R^9, C_{1-6}alkyl substituted with hydroxyl and R^9, C_{2-6}alkenyl substituted with R^9, C_{2-6}alkynyl substituted with R^9, C_{1-6}alkyl substituted with —$NR^{10}R^{11}$, C_{2-6}alkenyl substituted with —$NR^{10}R^{11}$, C_{2-6}alkynyl substituted with —$NR^{10}R^{11}$, C_{1-6}alkyl substituted with hydroxyl and —$NR^{10}R^{11}$, C_{1-6}alkyl substituted with one or two halogens and —$NR^{10}R^{11}$, —C_{1-6}alkyl-C(R^{12})═N—O—R^{12}, C_{1-6}alkyl substituted with —C(═O)—$NR^{10}R^{11}$, C_{1-6}alkyl substituted with —O—C(═O)—$NR^{10}R^{11}$, —S(═O)$_2$—C_{1-6}alkyl, —S(═O)$_2$-haloC_{1-6}alkyl, —S(═O)$_2$—$NR^{14}R^{15}$, C_{1-6}alkyl substituted with —S(═O)$_2$—C_{1-6}alkyl, C_{1-6}alkyl substituted with —S(═O)$_2$-haloC_{1-6}alkyl, C_{1-6}alkyl substituted with —S(═O)$_2$—$NR^{14}R^{15}$, C_{1-6}alkyl substituted with —NR^{12}—S(═O)$_2$—C_{1-6}alkyl, C_{1-6}alkyl substituted with —NH—S(═O)$_2$-haloC_{1-6}alkyl, C_{1-6}alkyl substituted with

—NR^{12}—S(═O)$_2$—NR^{14}R^{15}, R^{13}, C$_{1-6}$alkyl substituted with —P(═O)(OH)$_2$ or C$_{1-6}$alkyl substituted with —P(═O)(OC$_{1-6}$alkyl)$_2$;

R^{3b} represents hydrogen or hydroxyl; provided that if R^{3a} represents —NR^{10}R^{11}, then R^{3b} represents hydrogen; or

R^{3a} and R^{3b} are taken together to form ═O, to form ═NR^{10}, to form cyclopropyl together with the carbon atom to which they are attached, to form ═CH—C$_{0-4}$alkyl substituted with R^{3c}, or to form



wherein ring A is a monocyclic 5 to 7 membered saturated heterocycle containing one heteroatom selected from N, O or S, said heteroatom not being positioned in alpha position of the double bond, wherein ring A is optionally being substituted with cyano, C$_{1-4}$alkyl, hydroxyC$_{1-4}$alkyl, (C$_{1-4}$alkyl)NH—C$_{1-4}$alkyl, (C$_{1-4}$alkyl)$_2$N—C$_{1-4}$alkyl, haloC$_{1-4}$alkyl)NH—C$_{1-4}$alkyl, C$_{1-4}$alkoxyC$_{1-4}$alkyl, —C(═O)—NH$_2$, —C(═O)—NH(C$_{1-4}$alkyl), —C(═O)—N(C$_{1-4}$alkyl)$_2$;

R^{3b} represents hydrogen, hydroxyl, C$_{1-6}$alkoxy, R^9, —NR^{10}R^{11}, cyano, —C(═O)—C$_{1-6}$alkyl or —CH(OH)—C$_{1-6}$alkyl;

R^3 represents hydroxyl, C$_{1-6}$alkoxy, hydroxyC$_{1-6}$alkoxy, C$_{1-6}$alkoxy substituted with —NR^{10}R^{11}, C$_{1-6}$alkyl, C$_{2-6}$alkenyl, C$_{2-6}$alkynyl, haloC$_{1-6}$alkyl optionally substituted with —O—C(═O)—C$_{1-6}$alkyl, hydroxyC$_{1-6}$alkyl optionally substituted with —O—C(═O)—C$_{1-6}$alkyl, hydroxyC$_{2-6}$alkenyl, hydroxyC$_{2-6}$alkynyl, hydroxyhaloC$_{1-6}$alkyl, cyanoC$_{1-6}$alkyl, C$_{1-6}$alkyl substituted with carboxyl, C$_{1-6}$alkyl substituted with —C(═O)—C$_{1-6}$alkyl, C$_{1-6}$alkyl substituted with —C(═O)—O—C$_{1-6}$alkyl, C$_{1-6}$alkyl substituted with C$_{1-6}$alkoxyC$_{1-6}$alkyl-O—C(═O)—, C$_{1-6}$alkyl substituted with C$_{1-6}$alkoxyC$_{1-6}$alkyl-C(═O)—, C$_{1-6}$alkyl substituted with —O—C(═O)—C$_{1-6}$alkyl, C$_{1-6}$alkoxyC$_{1-6}$alkyl wherein each C$_{1-6}$alkyl may optionally be substituted with one or two hydroxyl groups or with —O—C(═O)—C$_{1-6}$alkyl, C$_{2-6}$alkenyl substituted with C$_{1-6}$alkoxy, C$_{2-6}$alkynyl substituted with C$_{1-6}$alkoxy, C$_{1-6}$alkyl substituted with R^9 and optionally substituted with —O—C(═O)—C$_{1-6}$alkyl, C$_{1-6}$alkyl substituted with —C(═O)—R^9, C$_{1-6}$alkyl substituted with hydroxyl and R^9, C$_{2-6}$alkenyl substituted with R^9, C$_{2-6}$alkynyl substituted with R^9, C$_{1-6}$alkyl substituted with —NR^{10}R^{11}, C$_{2-6}$alkenyl substituted with —NR^{10}R^{11}, C$_{2-6}$alkynyl substituted with —NR^{10}R^{11}, C$_{1-6}$alkyl substituted with hydroxyl and —NR^{10}R^{11}, C$_{1-6}$alkyl substituted with one or two halogens and —NR^{10}R^{11}, —C$_{1-6}$alkyl-C(R^{12})═N—O—R^{12}, C$_{1-6}$alkyl substituted with —C(═O)—NR^{10}R^{11}, C$_{1-6}$alkyl substituted with —O—C(═O)—NR^{10}R^{11}, —S(═O)$_2$—C$_{1-6}$alkyl, —S(═O)$_2$-haloC$_{1-6}$alkyl, —S(═O)$_2$—NR^{14}R^{15}, C$_{1-6}$alkyl substituted with —S(═O)$_2$—C$_{1-6}$alkyl, C$_{1-6}$alkyl substituted with —S(═O)$_2$-haloC$_{1-6}$alkyl, C$_{1-6}$alkyl substituted with —S(═O)$_2$—NR^{14}R^{15}, C$_{1-6}$alkyl substituted with —NR^{12}—S(═O)$_2$—C$_{1-6}$alkyl, C$_{1-6}$alkyl substituted with —NH—S(═O)$_2$-haloC$_{1-6}$alkyl, C$_{1-6}$alkyl substituted with —NR^{12}—S(═O)$_2$—NR^{14}R^{15}, R^{13}, C$_{1-6}$alkyl substituted with —P(═O)(OH)$_2$ or C$_{1-6}$alkyl substituted with —P(═O)(OC$_{1-6}$alkyl)$_2$;

R^4 and R^5 each independently represent hydrogen, C$_{1-6}$alkyl, C$_{1-6}$alkyl substituted with —NR^{14}R^{15}, hydroxyC$_{1-6}$alkyl, haloC$_{1-6}$alkyl, hydroxyhaloC$_{1-6}$alkyl, C$_{1-6}$alkoxyC$_{1-6}$alkyl wherein each C$_{1-6}$alkyl may optionally be substituted with one or two hydroxyl groups, —S(═O)$_2$—C$_{1-6}$alkyl, —S(═O)$_2$-haloC$_{1-6}$alkyl, —S(═O)$_2$—NR^{14}R^{15}, —C(═O)—NR^{14}R^{15}, —C(═O)—O—C$_{1-6}$alkyl, —C(═O)—R^{13}, C$_{1-6}$alkyl substituted with —S(═O)$_2$—C$_{1-6}$alkyl, C$_{1-6}$alkyl substituted with —S(═O)$_2$-haloC$_{1-6}$alkyl, C$_{1-6}$alkyl substituted with —S(═O)$_2$—NR^{14}R^{15}, C$_{1-6}$alkyl substituted with —NH—S(═O)$_2$—C$_{1-6}$alkyl, C$_{1-6}$alkyl substituted with —NH—S(═O)$_2$-haloC$_{1-6}$alkyl, C$_{1-6}$alkyl substituted with —NH—S(═O)$_2$—NR^{14}R^{15}, R^{13} or C$_{1-6}$alkyl substituted with R^{13};

R^6 represents C$_{3-8}$cycloalkyl, C$_{3-8}$cycloalkenyl, phenyl, 4 to 7-membered monocyclic heterocyclyl containing at least one heteroatom selected from N, O or S; said C$_{3-8}$cycloalkyl, C$_{3-8}$cycloalkenyl, phenyl, 4 to 7-membered monocyclic heterocyclyl, optionally and each independently being substituted by 1, 2, 3, 4 or 5 substituents, each substituent independently being selected from cyano, C$_{1-6}$alkyl, cyanoC$_{1-6}$alkyl, hydroxyl, carboxyl, hydroxyC$_{1-6}$alkyl, halogen, haloC$_{1-6}$alkyl, hydroxyhaloC$_{1-6}$alkyl, C$_{1-6}$alkoxy, C$_{1-6}$alkoxyC$_{1-6}$alkyl, C$_{1-6}$alkyl-O—C(═O)—, —NR^{14}R^{15}, —C(═O)—NR^{14}R^{15}, C$_{1-6}$alkyl substituted with —NR^{14}R^{15}, C$_{1-6}$alkyl substituted with —C(═O)—NR^{14}R^{15}, —S(═O)$_2$—C$_{1-6}$alkyl, —S(═O)$_2$-haloC$_{1-6}$alkyl, —S(═O)$_2$—NR^{14}R^{15}, C$_{1-6}$alkyl substituted with —S(═O)$_2$—C$_{1-6}$alkyl, C$_{1-6}$alkyl substituted with —S(═O)$_2$-haloC$_{1-6}$alkyl, C$_{1-6}$alkyl substituted with —S(═O)$_2$—NR^{14}R^{15}, C$_{1-6}$alkyl substituted with —NH—S(═O)$_2$—C$_{1-6}$alkyl, C$_{1-6}$alkyl substituted with —NH—S(═O)$_2$-haloC$_{1-6}$alkyl or C$_{1-6}$alkyl substituted with —NH—S(═O)$_2$—NR^{14}R^{15};

R^7 and R^8 each independently represent hydrogen, C$_{1-6}$alkyl, hydroxyC$_{1-6}$alkyl, haloC$_{1-6}$alkyl, hydroxyhaloC$_{1-6}$alkyl or C$_{1-6}$alkoxyC$_{1-6}$alkyl;

R^9 represents C$_{3-8}$cycloalkyl, C$_{3-8}$cycloalkenyl, phenyl, naphthyl, or 3 to 12 membered monocyclic or bicyclic heterocyclyl containing at least one heteroatom selected from N, O or S, said C$_{3-8}$cycloalkyl, C$_{3-8}$cycloalkenyl, phenyl, naphthyl, or 3 to 12 membered monocyclic or bicyclic heterocyclyl each optionally and each independently being substituted with 1, 2, 3, 4 or 5 substituents, each substituent independently being selected from ═O, C$_{1-4}$alkyl, hydroxyl, carboxyl, hydroxyC$_{1-4}$alkyl, cyano, cyanoC$_{1-4}$alkyl, C$_{1-4}$alkyl-O—C(═O)—, C$_{1-4}$alkyl substituted with C$_{1-4}$alkyl-O—C(═O)—, C$_{1-4}$alkyl-C(═O)—, C$_{1-4}$alkoxyC$_{1-4}$alkyl wherein each C$_{1-4}$alkyl may optionally be substituted with one or two hydroxyl groups, halogen, haloC$_{1-4}$alkyl, hydroxyhaloC$_{1-4}$alkyl, —NR^{14}R^{15}, —C(═O)—NR^{14}R^{15}, C$_{1-4}$alkyl substituted with —NR^{14}R^{15}, C$_{1-4}$alkyl substituted with —C(═O)—NR^{14}R^{15}, —S(═O)$_2$—C$_{1-4}$alkyl, —S(═O)$_2$-haloC$_{1-4}$alkyl, —S(═O)$_2$—NR^{14}R^{15}, C$_{1-4}$alkyl substituted with —S(═O)$_2$—NR^{14}R^{15}, C$_{1-4}$alkyl substituted with —NH—S(═O)$_2$—C$_{1-4}$alkyl, C$_{1-4}$alkyl substituted with —NH—S(═O)$_2$-haloC$_{1-4}$alkyl, C$_{1-4}$alkyl substituted with —NH—S(═O)$_2$—NR^{14}R^{15}, R^{13}, —C(═O)—R^{13}, C$_{1-4}$alkyl substituted with R^{13}, phenyl optionally substituted with R^{16}, phenylC$_{1-6}$alkyl wherein the phenyl is optionally substituted with R^{16}, a 5 or 6-membered aromatic monocyclic heterocyclyl containing at least one heteroatom selected from N, O or S wherein said heterocyclyl is optionally substituted with R^{16}; or when two of the substituents of R^9 are attached to the same atom, they may be taken together to form a 4 to 7-membered saturated monocyclic heterocyclyl containing at least one heteroatom selected from N, O or S;

R^{10} and R^{11} each independently represent hydrogen, carboxyl, C$_{1-6}$alkyl, cyanoC$_{1-6}$alkyl, C$_{1-6}$alkyl substituted with

$-NR^{14}R^{15}$, C_{1-6}alkyl substituted with $-C(=O)-NR^{14}R^{15}$, haloC_{1-6}alkyl, hydroxyC_{1-6}alkyl, hydroxyhaloC_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl wherein each C_{1-6}alkyl may optionally be substituted with one or two hydroxyl groups, R^6, C_{1-6}alkyl substituted with R^6, $-C(=O)-R^6$, $-C(=O)-C_{1-6}$alkyl, $-C(=O)$-hydroxyC_{1-6}alkyl, $-C(=O)$-haloC_{1-6}alkyl, $-C(=O)$-hydroxyhaloC_{1-6}alkyl, C_{1-6}alkyl substituted with $-Si(CH_3)_3$, $-S(=O)_2-C_{1-6}$alkyl, $-S(=O)_2$-haloC_{1-6}alkyl, $-S(=O)_2-NR^{14}R^{15}$, C_{1-6}alkyl substituted with $-S(=O)_2-C_{1-6}$alkyl, C_{1-6}alkyl substituted with $-S(=O)_2$-haloC_{1-6}alkyl, C_{1-6}alkyl substituted with $-S(=O)_2-NR^{14}R^{15}$, C_{1-6}alkyl substituted with $-NH-S(=O)_2-C_{1-6}$alkyl, C_{1-6}alkyl substituted with $-NH-S(=O)_2$-haloC_{1-6}alkyl, C_{1-6}alkyl substituted with carboxyl, or C_{1-6}alkyl substituted with $-NH-S(=O)_2-NR^{14}R^{15}$;

R^{12} represents hydrogen or C_{1-4}alkyl optionally substituted with C_{1-4}alkoxy;

R^{13} represents C_{3-8}cycloalkyl or a saturated 4 to 6-membered monocyclic heterocyclyl containing at least one heteroatom selected from N, O or S, wherein said C_{3-8}cycloalkyl or monocyclic heterocyclyl is optionally substituted with 1, 2 or 3 substituents each independently selected from halogen, hydroxyl, C_{1-6}alkyl, haloC_{1-6}alkyl, $=O$, cyano, $-C(=O)-C_{1-6}$alkyl, C_{1-6}alkoxy, or $-NR^{14}R^{15}$;

R^{14} and R^{15} each independently represent hydrogen, or haloC_{1-4}alkyl, or C_{1-4}alkyl optionally substituted with a substituent selected from hydroxyl, C_{1-4}alkoxy, amino or mono- or di(C_{1-4}alkyl)amino;

R^{16} represents hydroxyl, halogen, cyano, C_{1-4}alkyl, C_{1-4}alkoxy, $-NR^{14}R^{15}$ or $-C(=O)NR^{14}R^{15}$;

R^{18} represents hydrogen, C_{1-6} alkyl, C_{3-8} cycloalkyl, C_{1-4}alkyl substituted with C_{3-8} cycloalkyl;

R^{19} represents hydrogen; C_{1-6} alkyl; C_{3-8} cycloalkyl; C_{1-6}alkyl substituted with $-O-R^{20}$; $-(CH_2)_r-CN$; $-(CH_2)$, $-CONR^{20}R^{21}$; $-(CH_2)_{r1}-NR^{20}R^{21}$; $-(CH_2)_{r1}-NR^{20}CO_2R^{21}$; $-(CH_2)_{r1}-NR^{20}$; $-(CH_2)_s-SO_2-R^{21}$; $-(CH_2)_{r1}-NH-SO_2-NR^{20}R^{21}$; $-(CH_2)_{r1}-NR^{20}CO_2R^{21}-(CH_2)_r-SO_2NR^{20}R^{21}$; phenyl optionally substituted with 1, 2, 3, 4 or 5 substituents each independently selected from halogen, C_{1-4}alkyl, C_{1-4}alkyloxy, cyano or amino; a 5- or 6-membered aromatic monocyclic heterocycle containing at least one heteroatom selected from N, O or S, said heterocycle being optionally substituted with 1, 2, 3 or 4 substituents each independently selected from halogen, C_{1-4}alkyl, C_{1-4}alkyloxy, cyano or amino; wherein said C_{1-6} alkyl and C_{3-8} cycloalkyl, may be optionally substituted by one or more R^{20} groups

R^{20} and R^{21} independently represent hydrogen, C_{1-6} alkyl, hydroxyC_{1-6}alkyl, $-(CH_2)_n-O-C_{1-6}$alkyl, or when attached to a nitrogen atom R^{20} and R^{21} can be taken together to form with the nitrogen atom to which they are attached a monocyclic saturated 4, 5 or 6-membered ring which optionally contains a further heteroatom selected from O, S or N;

R^{22} and R^{23} independently represent hydrogen, C_{1-6} alkyl, or hydroxyC_{1-6}alkyl;

m independently represents an integer equal to 0, 1 or 2;

n independently represents an integer equal to 0, 1, 2, 3 or 4;

s independently represents an integer equal to 0, 1, 2, 3 or 4;

r independently represent an integer equal to 1, 2, 3, or 4;

r1 independently represent an integer equal to 2, 3 or 4;

the N-oxides thereof, the pharmaceutically acceptable salts thereof or the solvates thereof.

WO2006/092430, WO2008/003702, WO01/68047, WO2005/007099, WO2004/098494, WO2009/141386, WO 2004/030635, WO 2008/141065, WO 2011/026579, WO 2011/028947, WO 2007/003419, WO 00/42026, WO2011/146591 and WO2011/135376 which each disclose a series of heterocyclyl derivatives.

DETAILED DESCRIPTION OF THE INVENTION

Unless the context indicates otherwise, references to formula (I) in all sections of this document (including the uses, methods and other aspects of the invention) include references to all other sub-formula (e.g. Ia), sub-groups, preferences, embodiments and examples as defined herein.

The prefix "C_{x-y}" (where x and y are integers) as used herein refers to the number of carbon atoms in a given group. Thus, a C_{1-6}alkyl group contains from 1 to 6 carbon atoms, a C_{3-6}cycloalkyl group contains from 3 to 6 carbon atoms, a C_{1-4}alkoxy group contains from 1 to 4 carbon atoms, and so on.

The term 'halo' or 'halogen' as used herein refers to a fluorine, chlorine, bromine or iodine atom.

The term 'C_{1-4}alkyl', or 'C_{1-6}alkyl' as used herein as a group or part of a group refers to a linear or branched saturated hydrocarbon group containing from 1 to 4 or 1 to 6 carbon atoms. Examples of such groups include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, isopentyl, neopentyl or hexyl and the like.

The term 'C_{2-4}alkenyl' or 'C_{2-6}alkenyl' as used herein as a group or part of a group refers to a linear or branched hydrocarbon group containing from 2 to 4 or 2 to 6 carbon atoms and containing a carbon carbon double bond.

The term 'C_{2-4}alkenediyl' used herein as a group or part of a group refers to a linear or branched bivalent hydrocarbon group containing from 2 to 4 carbon atoms and containing a carbon carbon double bond.

The term 'C_{2-4}alkynyl' or 'C_{2-6}alkynyl' as used herein as a group or part of a group refers to a linear or branched hydrocarbon group having from 2 to 4 or 2 to 6 carbon atoms and containing a carbon carbon triple bond.

The term 'C_{1-4}alkoxy' or 'C_{1-6}alkoxy' as used herein as a group or part of a group refers to an $O-C_{1-4}$alkyl group or an $O-C_{1-6}$alkyl group wherein C_{1-4}alkyl and C_{1-6}alkyl are as defined herein. Examples of such groups include methoxy, ethoxy, propoxy, butoxy, and the like.

The term 'C_{1-4}alkoxyC_{1-4}alkyl' or 'C_{1-6}alkoxyC_{1-6}alkyl' as used herein as a group or part of a group refers to a C_{1-4}alkyl-O$-C_{1-4}$alkyl group or a C_{1-6}alkyl-O$-C_{1-6}$alkyl group wherein C_{1-4}alkyl and C_{1-6}alkyl are as defined herein. Examples of such groups include methoxyethyl, ethoxyethyl, propoxymethyl, butoxypropyl, and the like.

The term 'C_{3-8}cycloalkyl' as used herein refers to a saturated monocyclic hydrocarbon ring of 3 to 8 carbon atoms. Examples of such groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or cyclooctyl and the like.

The term 'C_{3-8}cycloalkenyl' as used herein refers to a monocyclic hydrocarbon ring of 3 to 8 carbon atoms having a carbon carbon double bond.

The term 'hydroxyC_{1-4}alkyl' or 'hydroxyC_{1-6}alkyl' as used herein as a group or part of a group refers to a C_{1-4}alkyl or C_{1-6}alkyl group as defined herein wherein one or more than one hydrogen atom is replaced with a hydroxyl group. The terms 'hydroxyC_{1-4}alkyl' or 'hydroxyC_{1-6}alkyl' therefore include monohydroxyC_{1-4}alkyl, monohydroxyC_{1-6}alkyl and also polyhydroxyC_{1-4}alkyl and polyhydroxyC_{1-}

$_{6}$alkyl. There may be one, two, three or more hydrogen atoms replaced with a hydroxyl group, so the hydroxy-C_{1-4}alkyl or hydroxyC_{1-6}alkyl may have one, two, three or more hydroxyl groups. Examples of such groups include hydroxymethyl, hydroxyethyl, hydroxypropyl and the like.

The term 'haloC_{1-4}alkyl' or 'haloC_{1-6}alkyl' as used herein as a group or part of a group refers to a C_{1-4}alkyl or C_{1-6}alkyl group as defined herein wherein one or more than one hydrogen atom is replaced with a halogen. The term 'haloC_{1-4}alkyl' or 'haloC_{1-6}alkyl' therefore include monohaloC_{1-4}alkyl, monohaloC_{1-6}alkyl and also polyhalo-C_{1-4}alkyl and polyhaloC_{1-6}alkyl. There may be one, two, three or more hydrogen atoms replaced with a halogen, so the haloC_{1-4}alkyl or haloC_{1-6}alkyl may have one, two, three or more halogens. Examples of such groups include fluoroethyl, fluoromethyl, trifluoromethyl or trifluoroethyl and the like.

The term 'hydroxyhaloC_{1-4}alkyl' or 'hydroxyhalo-C_{1-6}alkyl' as used herein as a group or part of a group refers to a C_{1-4}alkyl or C_{1-6}alkyl group as defined herein wherein one or more than one hydrogen atom is replaced with a hydroxyl group and one or more than one hydrogen atom is replaced with a halogen. The term 'hydroxyhaloC_{1-4}alkyl' or 'hydroxyhaloC_{1-6}alkyl' therefore refers to a C_{1-4}alkyl or C_{1-6}alkyl group wherein one, two, three or more hydrogen atoms are replaced with a hydroxyl group and one, two, three or more hydrogen atoms are replaced with a halogen.

The term 'hydroxyC_{1-4}alkoxy' or 'hydroxyC_{1-6}alkoxy' as used herein as a group or part of a group refers to an O—C_{1-4}alkyl group or an O—C_{1-6}alkyl group wherein the C_{1-4}alkyl and C_{1-6}alkyl group is as defined above and one or more than one hydrogen atom of the C_{1-4}alkyl or C_{1-6}alkyl group is replaced with a hydroxyl group. The term 'hydroxyC_{1-4}alkoxy' or 'hydroxyC_{1-6}alkoxy' therefore include monohydroxyC_{1-4}alkoxy, monohydroxyC_{1-6}alkoxy and also polyhydroxyC_{1-4}alkoxy and polyhydroxy-C_{1-6}alkoxy. There may be one, two, three or more hydrogen atoms replaced with a hydroxyl group so the hydroxy-C_{1-4}alkoxy or hydroxyC_{1-6}alkoxy may have one, two, three or more hydroxyl groups. Examples of such groups include hydroxymethoxy, hydroxyethoxy, hydroxypropoxy and the like.

The term 'haloC_{1-4}alkoxy' or 'haloC_{1-6}alkoxy' as used herein as a group or part of a group refers to a O—C_{1-4}alkyl group or a O—C_{1-6} alkyl group as defined herein wherein one or more than one hydrogen atom is replaced with a halogen. The terms 'haloC_{1-4}alkoxy' or 'haloC_{1-6}alkoxy' therefore include monohaloC_{1-4}alkoxy, monohalo-C_{1-6}alkoxy and also polyhaloC_{1-4}alkoxy and polyhalo-C_{1-6}alkoxy. There may be one, two, three or more hydrogen atoms replaced with a halogen, so the haloC_{1-4}alkoxy or haloC_{1-6}alkoxy may have one, two, three or more halogens. Examples of such groups include fluoroethyloxy, difluoromethoxy or trifluoromethoxy and the like.

The term 'hydroxyhaloC_{1-4}alkoxy' as used herein as a group or part of a group refers to an O—C_{1-4}alkyl group wherein the C_{1-4}alkyl group is as defined herein and wherein one or more than one hydrogen atom is replaced with a hydroxyl group and one or more than one hydrogen atom is replaced with a halogen. The term 'hydroxyhaloC_{1-4}alkoxy' therefore refers to a O—C_{1-4}alkyl group wherein one, two, three or more hydrogen atoms are replaced with a hydroxyl group and one, two, three or more hydrogen atoms are replaced with a halogen.

The term 'haloC_{1-4}alkoxyC_{1-4}alkyl' as used herein as a group or part of a group refers to a C_{1-4}alkyl-O—C_{1-4}alkyl group wherein C_{1-4}alkyl is as defined herein and wherein in one or both of the C_{1-4}alkyl groups one or more than one hydrogen atom is replaced with a halogen. The term 'haloC_{1-4} alkoxyC_{1-4}alkyl' therefore refers to a C_{1-4}alkyl-O—C_{1-4}alkyl group wherein in one or both of the C_{1-4}alkyl groups one, two, three or more hydrogen atoms are replaced with a halogen and wherein C_{1-4} alkyl is as defined herein. Preferably, in one of the C_{1-4}alkyl groups one or more than one hydrogen atom is replaced with a halogen. Preferably, haloC_{1-4}alkoxyC_{1-4}alkyl means C_{1-4}alkyl substituted with haloC_{1-4}alkoxy.

The term 'hydroxyhaloC_{1-4}alkoxyC_{1-4}alkyl' as used herein refers to a C_{1-4}alkyl-O—C_{1-4}alkyl group wherein C_{1-4}alkyl is as defined herein and wherein in one or both of the C_{1-4}alkyl groups one or more than one hydrogen atom is replaced with a hydroxyl group and one or more than one hydrogen atom is replaced with a halogen. The terms 'hydroxyhaloC_{1-4}alkoxyC_{1-4}alkyl' therefore refers to a C_{1-4}alkyl-O—C_{1-4}alkyl group wherein in one or both of the C_{1-4}alkyl groups one, two, three or more hydrogen atoms are replaced with a hydroxyl group and one, two, three or more hydrogen atoms are replaced with a halogen and wherein C_{1-4}alkyl is as defined herein.

The term 'hydroxyC_{2-6}alkenyl' as used herein refers to a C_{2-6}alkenyl group wherein one or more than one hydrogen atom is replaced with a hydroxyl group and wherein C_{2-6}alkenyl is as defined herein.

The term 'hydroxyC_{2-6}alkynyl' as used herein refers to a C_{2-6}alkynyl group wherein one or more than one hydrogen atom is replaced with a hydroxyl group and wherein C_{2-6}alkynyl is as defined herein.

The term phenylC_{1-6}alkyl as used herein refers to a C_{1-6}alkyl group as defined herein which is substituted with one phenyl group.

The term cyanoC_{1-4}alkyl or cyanoC_{1-6}alkyl as used herein refers to a C_{1-4}alkyl or C_{1-6}alkyl group as defined herein which is substituted with one cyano group.

The term "heterocyclyl" as used herein shall, unless the context indicates otherwise, include both aromatic and non-aromatic ring systems. Thus, for example, the term "heterocyclyl group" includes within its scope aromatic, non-aromatic, unsaturated, partially saturated and fully saturated heterocyclyl ring systems. In general, unless the context indicates otherwise, such groups may be monocyclic or bicyclic and may contain, for example, 3 to 12 ring members, more usually 5 to 10 ring members. Reference to 4 to 7 ring members include 4, 5, 6 or 7 atoms in the ring and reference to 4 to 6 ring members include 4, 5, or 6 atoms in the ring. Examples of monocyclic groups are groups containing 3, 4, 5, 6, 7 and 8 ring members, more usually 3 to 7, and preferably 5, 6 or 7 ring members, more preferably 5 or 6 ring members. Examples of bicyclic groups are those containing 8, 9, 10, 11 and 12 ring members, and more usually 9 or 10 ring members. Where reference is made herein to heterocyclyl groups, the heterocyclyl ring can, unless the context indicates otherwise, be optionally substituted (i.e. unsubstituted or substituted) by one or more substituents as discussed herein.

The heterocyclyl groups can be heteroaryl groups having from 5 to 12 ring members, more usually from 5 to 10 ring members. The term "heteroaryl" is used herein to denote a heterocyclyl group having aromatic character. The term "heteroaryl" embraces polycyclic (e.g. bicyclic) ring systems wherein one or more rings are non-aromatic, provided that at least one ring is aromatic. In such polycyclic systems, the group may be attached by the aromatic ring, or by a non-aromatic ring.

Examples of heteroaryl groups are monocyclic and bicyclic groups containing from five to twelve ring members, and more usually from five to ten ring members. The heteroaryl group can be, for example, a five membered or six membered monocyclic ring or a bicyclic structure formed from fused five and six membered rings or two fused six membered rings, or two fused five membered rings. Each ring may contain up to about five heteroatoms typically selected from nitrogen, sulphur and oxygen. Typically the heteroaryl ring will contain up to 4 heteroatoms, more typically up to 3 heteroatoms, more usually up to 2, for example a single heteroatom. In one embodiment, the heteroaryl ring contains at least one ring nitrogen atom. The nitrogen atoms in the heteroaryl rings can be basic, as in the case of an imidazole or pyridine, or essentially non-basic as in the case of an indole or pyrrole nitrogen. In general the number of basic nitrogen atoms present in the heteroaryl group, including any amino group substituents of the ring, will be less than five.

Examples of five membered heteroaryl groups include but are not limited to pyrrole, furan, thiophene, imidazole, furazan, oxazole, oxadiazole, oxatriazole, isoxazole, thiazole, thiadiazole, isothiazole, pyrazole, triazole and tetrazole groups.

Examples of six membered heteroaryl groups include but are not limited to pyridine, pyrazine, pyridazine, pyrimidine and triazine.

A bicyclic heteroaryl group may be, for example, a group selected from:

a) a benzene ring fused to a 5- or 6-membered ring containing 1, 2 or 3 ring heteroatoms;
b) a pyridine ring fused to a 5- or 6-membered ring containing 0, 1, 2 or 3 ring heteroatoms;
c) a pyrimidine ring fused to a 5- or 6-membered ring containing 0, 1 or 2 ring heteroatoms;
d) a pyrrole ring fused to a 5- or 6-membered ring containing 0, 1, 2 or 3 ring heteroatoms;
e) a pyrazole ring fused to a 5- or 6-membered ring containing 0, 1 or 2 ring heteroatoms;
f) an imidazole ring fused to a 5- or 6-membered ring containing 0, 1 or 2 ring heteroatoms;
g) an oxazole ring fused to a 5- or 6-membered ring containing 0, 1 or 2 ring heteroatoms;
h) an isoxazole ring fused to a 5- or 6-membered ring containing 0, 1 or 2 ring heteroatoms;
i) a thiazole ring fused to a 5- or 6-membered ring containing 0, 1 or 2 ring heteroatoms;
j) an isothiazole ring fused to a 5- or 6-membered ring containing 0, 1 or 2 ring heteroatoms;
k) a thiophene ring fused to a 5- or 6-membered ring containing 0, 1, 2 or 3 ring heteroatoms;
l) a furan ring fused to a 5- or 6-membered ring containing 0, 1, 2 or 3 ring heteroatoms;
m) a cyclohexyl ring fused to a 5- or 6-membered ring containing 1, 2 or 3 ring heteroatoms; and
n) a cyclopentyl ring fused to a 5- or 6-membered ring containing 1, 2 or 3 ring heteroatoms.

Particular examples of bicyclic heteroaryl groups containing a five membered ring fused to another five membered ring include but are not limited to imidazothiazole (e.g. imidazo[2,1-b]thiazole) and imidazoimidazole (e.g. imidazo [1,2-a]imidazole).

Particular examples of bicyclic heteroaryl groups containing a six membered ring fused to a five membered ring include but are not limited to benzofuran, benzothiophene, benzimidazole, benzoxazole, isobenzoxazole, benzisoxazole, benzthiazole, benzisothiazole, isobenzofuran, indole, isoindole, indolizine, indoline, isoindoline, purine (e.g., adenine, guanine), indazole, pyrazolopyrimidine (e.g. pyrazolo[1,5-a]pyrimidine), triazolopyrimidine (e.g. [1,2,4]triazolo[1,5-a]pyrimidine), benzodioxole, imidazopyridine and pyrazolopyridine (e.g. pyrazolo[1,5-a]pyridine) groups.

Particular examples of bicyclic heteroaryl groups containing two fused six membered rings include but are not limited to quinoline, isoquinoline, chroman, thiochroman, chromene, isochromene, chroman, isochroman, benzodioxan, quinolizine, benzoxazine, benzodiazine, pyridopyridine, quinoxaline, quinazoline, cinnoline, phthalazine, naphthyridine and pteridine groups.

Examples of polycyclic heteroaryl groups containing an aromatic ring and a non-aromatic ring include, tetrahydroisoquinoline, tetrahydroquinoline, dihydrobenzthiene, dihydrobenzfuran, 2,3-dihydro-benzo[1,4]dioxine, benzo[1,3]dioxole, 4,5,6,7-tetrahydrobenzofuran, tetrahydrotriazolopyrazine (e.g. 5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine), indoline and indane groups.

A nitrogen-containing heteroaryl ring must contain at least one ring nitrogen atom. Each ring may, in addition, contain up to about four other heteroatoms typically selected from nitrogen, sulphur and oxygen. Typically the heteroaryl ring will contain up to 3 heteroatoms, for example 1, 2 or 3, more usually up to 2 nitrogens, for example a single nitrogen. The nitrogen atoms in the heteroaryl rings can be basic, as in the case of an imidazole or pyridine, or essentially non-basic as in the case of an indole or pyrrole nitrogen. In general the number of basic nitrogen atoms present in the heteroaryl group, including any amino group substituents of the ring, will be less than five.

Examples of nitrogen-containing heteroaryl groups include, but are not limited to, pyridyl, pyrrolyl, imidazolyl, oxazolyl, oxadiazolyl, thiadiazolyl, oxatriazolyl, isoxazolyl, thiazolyl, isothiazolyl, furazanyl, pyrazolyl, pyrazinyl, pyrimidinyl, pyridazinyl, triazinyl, triazolyl (e.g., 1,2,3-triazolyl, 1,2,4-triazolyl), tetrazolyl, quinolinyl, isoquinolinyl, benzimidazolyl, benzoxazolyl, benzisoxazole, benzthiazolyl and benzisothiazole, indolyl, 3H-indolyl, isoindolyl, indolizinyl, isoindolinyl, purinyl (e.g., adenine [6-aminopurine], guanine [2-amino-6-hydroxypurine]), indazolyl, quinolizinyl, benzoxazinyl, benzodiazinyl, pyridopyridinyl, quinoxalinyl, quinazolinyl, cinnolinyl, phthalazinyl, naphthyridinyl and pteridinyl.

Examples of nitrogen-containing polycyclic heteroaryl groups containing an aromatic ring and a non-aromatic ring include tetrahydroisoquinolinyl, tetrahydroquinolinyl, and indolinyl.

The term "non-aromatic group" embraces, unless the context indicates otherwise, unsaturated ring systems without aromatic character, partially saturated and fully saturated heterocyclyl ring systems. The terms "unsaturated" and "partially saturated" refer to rings wherein the ring structure(s) contains atoms sharing more than one valence bond i.e. the ring contains at least one multiple bond e.g. a C═C, C≡C or N═C bond. The term "fully saturated" refers to rings where there are no multiple bonds between ring atoms. Saturated heterocyclyl groups include piperidine, morpholine, thiomorpholine, piperazine. Partially saturated heterocyclyl groups include pyrazolines, for example 2-pyrazoline and 3-pyrazoline.

Examples of non-aromatic heterocyclyl groups are groups having from 3 to 12 ring members, more usually 5 to 10 ring members. Such groups can be monocyclic or bicyclic, for example, and typically have from 1 to 5 heteroatom ring members (more usually 1, 2, 3 or 4 heteroatom ring members), usually selected from nitrogen, oxygen and sulphur. The heterocyclyl groups can contain, for example, cyclic ether moieties (e.g. as in tetrahydrofuran and dioxane), cyclic thioether moieties (e.g. as in tetrahydrothiophene and dithiane), cyclic amine moieties (e.g. as in pyrrolidine), cyclic amide moieties (e.g. as in pyrrolidone), cyclic thioamides, cyclic thioesters, cyclic ureas (e.g. as in imidazolidin-2-one) cyclic ester moieties (e.g. as in butyrolactone), cyclic sulphones (e.g. as in sulpholane and sulpholene), cyclic sulphoxides, cyclic sulphonamides and combinations thereof (e.g. thiomorpholine).

Particular examples include morpholine, piperidine (e.g. 1-piperidinyl, 2-piperidinyl, 3-piperidinyl and 4-piperidinyl), piperidone, pyrrolidine (e.g. 1-pyrrolidinyl, 2-pyrrolidinyl and 3-pyrrolidinyl), pyrrolidone, azetidine, pyran (2H-pyran or 4H-pyran), dihydrothiophene, dihydropyran, dihydrofuran, dihydrothiazole, tetrahydrofuran, tetrahydrothiophene, dioxane, tetrahydropyran (e.g. 4-tetrahydro pyranyl), imidazoline, imidazolidinone, oxazoline, thiazoline, 2-pyrazoline, pyrazolidine, piperazone, piperazine, and N-alkyl piperazines such as N-methyl piperazine. In general, preferred non-aromatic heterocyclyl groups include saturated groups such as piperidine, pyrrolidine, azetidine, morpholine, piperazine and N-alkyl piperazines.

In a nitrogen-containing non-aromatic heterocyclyl ring the ring must contain at least one ring nitrogen atom. The heterocylic groups can contain, for example cyclic amine moieties (e.g. as in pyrrolidine), cyclic amides (such as a pyrrolidinone, piperidone or caprolactam), cyclic sulphonamides (such as an isothiazolidine 1,1-dioxide, [1,2]thiazinane 1,1-dioxide or [1,2]thiazepane 1,1-dioxide) and combinations thereof.

Particular examples of nitrogen-containing non-aromatic heterocyclyl groups include aziridine, morpholine, thiomorpholine, piperidine (e.g. 1-piperidinyl, 2-piperidinyl, 3-piperidinyl and 4-piperidinyl), pyrrolidine (e.g. 1-pyrrolidinyl, 2-pyrrolidinyl and 3-pyrrolidinyl), pyrrolidone, dihydrothiazole, imidazoline, imidazolidinone, oxazoline, thiazoline, 6H-1,2,5-thiadiazine, 2-pyrazoline, 3-pyrazoline, pyrazolidine, piperazine, and N-alkyl piperazines such as N-methyl piperazine.

The heterocyclyl groups can be polycyclic fused ring systems or bridged ring systems such as the oxa- and aza analogues of bicycloalkanes, tricycloalkanes (e.g. adamantane and oxa-adamantane). For an explanation of the distinction between fused and bridged ring systems, see *Advanced Organic Chemistry*, by Jerry March, 4th Edition, Wiley Interscience, pages 131-133, 1992.

The heterocyclyl groups can each be unsubstituted or substituted by one or more substituent groups. For example, heterocyclyl groups can be unsubstituted or substituted by 1, 2, 3 or 4 substituents. Where the heterocyclyl group is monocyclic or bicyclic, typically it is unsubstituted or has 1, 2 or 3 substituents.

The term "carbocyclyl" as used herein shall, unless the context indicates otherwise, include both aromatic and non-aromatic ring systems. Thus, for example, the term "carbocyclyl group" includes within its scope aromatic, non-aromatic, unsaturated, partially saturated and fully saturated carbocyclyl ring systems. In general, unless the context indicates otherwise, such groups may be monocyclic or bicyclic and may contain, for example, 3 to 12 ring members, more usually 5 to 10 ring members. Reference to 4 to 7 ring members include 4, 5, 6 or 7 atoms in the ring and reference to 4 to 6 ring members include 4, 5, or 6 atoms in the ring. Examples of monocyclic groups are groups containing 3, 4, 5, 6, 7 and 8 ring members, more usually 3 to 7, and preferably 5, 6 or 7 ring members, more preferably 5 or 6 ring members. Examples of bicyclic groups are those containing 8, 9, 10, 11 and 12 ring members, and more usually 9 or 10 ring members. Where reference is made herein to carbocyclyl groups, the carbocyclyl ring can, unless the context indicates otherwise, be optionally substituted (i.e. unsubstituted or substituted) by one or more substituents as discussed herein.

The term carbocyclyl comprises aryl, C_{3-8}cycloalkyl, C_{3-8}cycloalkenyl.

The term aryl as used herein refers to carbocyclyl aromatic groups including phenyl, naphthyl, indenyl, and tetrahydronaphthyl groups.

Whenever used hereinbefore or hereinafter that substituents can be selected each independently out of a list of numerous definitions, all possible combinations are intended which are chemically possible. Whenever used hereinbefore or hereinafter that a particular substituent is further substituted with two or more groups, such as for example hydroxyhaloC_{1-4}alkyl, hydroxyhaloC_{1-4}alkoxy, all possible combinations are intended which are chemically possible.

In one embodiment, Y represents —CR^{18}═N—OR^{19}. In particular wherein R^{18} and R^{19} represent C_{1-6}alkyl.

In one embodiment, Y represents -E-D wherein E represents a bond.

In one embodiment, Y represents a 3 to 12 ring membered monocyclic or bicyclic carbocyclyl or a 3 to 12 ring membered monocyclic or bicyclic heterocyclyl containing at least one heteroatom selected from N, O or S, wherein said carbocyclyl and heterocyclyl may each be optionally substituted by one or more (e.g. 1, 2 or 3) R^1 groups.

In one embodiment, Y represents a 5 to 12 ring membered monocyclic or bicyclic carbocyclyl or a 5 to 12 ring membered monocyclic or bicyclic heterocyclyl containing at least one heteroatom selected from N, O or S, wherein said carbocyclyl and heterocyclyl may each be optionally substituted by one or more (e.g. 1, 2 or 3) R^1 groups.

In one embodiment, Y represents an aromatic 3 to 12, in particular an aromatic 5 to 12, ring membered monocyclic or bicyclic carbocyclyl or an aromatic 3 to 12, in particular an aromatic 5 to 12, ring membered monocyclic or bicyclic heterocyclyl containing at least one heteroatom selected from N, O or S, wherein said carbocyclyl and heterocyclyl may each be optionally substituted by one or more (e.g. 1, 2 or 3) R^1 groups.

In one embodiment, Y represents an aromatic 3 to 12 (e.g. 5 to 10) ring membered monocyclic or bicyclic carbocyclyl, wherein said carbocyclyl may be optionally substituted by one or more (e.g. 1, 2 or 3) R^1 groups.

In one embodiment, Y represents phenyl or naphthyl, wherein said phenyl or naphthyl may each be optionally substituted by one or more (e.g. 1, 2 or 3) R^1 groups.

In one embodiment, Y represents a 5 to 12 ring membered monocyclic or bicyclic heterocyclyl containing at least one heteroatom selected from N, O or S, wherein said heterocyclyl may each be optionally substituted by one or more (e.g. 1, 2 or 3) R^1 groups.

In one embodiment, Y represents an aromatic 5 to 12 ring membered monocyclic heterocyclyl containing at least one heteroatom selected from N, O or S, wherein said heterocyclyl group may each be optionally substituted by one or more (e.g. 1, 2 or 3) R^1 groups.

In one embodiment, Y represents a 5 or 6 ring membered monocyclic heterocyclyl containing at least one heteroatom selected from N, O or S, wherein said heterocyclyl may each be optionally substituted by one or more (e.g. 1, 2 or 3) R^1 groups.

In one embodiment, Y represents an aromatic 5 or 6 ring membered monocyclic heterocyclyl containing at least one heteroatom selected from N, O or S, wherein said heterocyclyl may each be optionally substituted by one or more (e.g. 1, 2 or 3) R^1 groups.

In one embodiment, Y represents a 5 ring membered monocyclic heterocyclyl containing at least one heteroatom selected from N, O or S, wherein said heterocyclyl may each be optionally substituted by one or more (e.g. 1, 2 or 3) R^1 groups.

In one embodiment, Y represents a 5 ring membered monocyclic aromatic heterocyclyl containing at least one heteroatom selected from N, O or S, wherein said heterocyclyl may each be optionally substituted by one or more (e.g. 1, 2 or 3) R^1 groups.

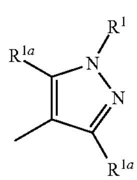
In one embodiment, Y represents pyrazolyl (e.g. pyrazol-4-yl), wherein said pyrazolyl may each be optionally substituted by one or more (e.g. 1, 2 or 3) R^1 groups.

In one embodiment, Y represents a 6 ring membered monocyclic heterocyclyl containing at least one heteroatom selected from N, O or S, wherein said heterocyclyl may each be optionally substituted by one or more (e.g. 1, 2 or 3) R^1 groups.

In one embodiment, Y represents a 6 ring membered monocyclic aromatic heterocyclyl containing at least one heteroatom selected from N, O or S, wherein said heterocyclyl may each be optionally substituted by one or more (e.g. 1, 2 or 3) R^1 groups.

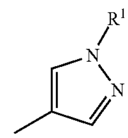
In one embodiment, Y represents a 12 ring membered bicyclic heterocyclyl containing at least one heteroatom selected from N, O or S, wherein said heterocyclyl may each be optionally substituted by one or more (e.g. 1, 2 or 3) R^1 groups.

In one embodiment, Y represents a 12 ring membered bicyclic aromatic heterocyclyl containing at least one heteroatom selected from N, O or S, wherein said heterocyclyl may each be optionally substituted by one or more (e.g. 1, 2 or 3) R^1 groups.



In one embodiment Y represents wherein R^1 represents hydrogen, C_{1-6}alkyl, C_{2-4}alkenyl, hydroxyC_{1-6}alkyl, haloC_{1-6}alkyl, hydroxyhaloC_{1-6}alkyl, cyanoC_{1-4}alkyl, C_{1-6}alkoxyC_{1-6}alkyl wherein each C_{1-6}alkyl may optionally be substituted with one or two hydroxyl groups, C_{1-6}alkyl substituted with —NR^4R^5, C_{1-6}alkyl substituted with —C(═O)—NR^4R^5, —S(═O)$_2$—C_{1-6}alkyl, —S(═O)$_2$-haloC_{1-6}alkyl, —S(═O)$_2$—$NR^{14}R^{15}$, C_{1-6}alkyl substituted with —S(═O)$_2$—C_{1-6}alkyl, C_{1-6}alkyl substituted with —S(═O)$_2$-haloC_{1-6}alkyl, C_{1-6}alkyl substituted with —S(═O)$_2$—$NR^{14}R^{15}$, C_{1-6}alkyl substituted with —NH—S(═O)$_2$—C_{1-6}alkyl, C_{1-6}alkyl substituted with —NH—S(═O)$_2$-haloC_{1-6}alkyl, C_{1-6}alkyl substituted with —NR^{12}—S(═O)$_2$—$NR^{14}R^{15}$, R^6, C_{1-6}alkyl substituted with R^6, C_{1-6}alkyl substituted with —C(═O)—R^6, hydroxyC_{1-6}alkyl substituted with R^6, C_{1-6}alkyl substituted with —Si$(CH_3)_3$, C_{1-6}alkyl substituted with —P(═O)$(OH)_2$ or C_{1-6}alkyl substituted with —P(═O)$(OC_{1-6}alkyl)_2$; and each R^{1a} is independently selected from hydrogen, C_{1-4}alkyl, hydroxyC_{1-4}alkyl, C_{1-4}alkyl substituted with amino or mono- or di(C_{1-4}alkyl)amino or —NH(C_{3-8}cycloalkyl), cyanoC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, and C_{1-4}alkyl substituted with one or more fluoro atoms. In one embodiment R^{1a} is independently selected from hydrogen and C_{1-4}alkyl. In one embodiment R^{1a} is hydrogen.

In one embodiment, Y represents



wherein R^1 represents hydrogen, C_{1-6}alkyl, C_{2-4}alkenyl, hydroxyC_{1-6}alkyl, haloC_{1-6}alkyl, hydroxyhaloC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkyl wherein each C_{1-6}alkyl may optionally be substituted with one or two hydroxyl groups, C_{1-6}alkyl substituted with —NR^4R^5, C_{1-6}alkyl substituted with —C(═O)—NR^4R^5, —S(═O)$_2$—C_{1-6}alkyl, —S(═O)$_2$-haloC_{1-6}alkyl, —S(═O)$_2$—$NR^{14}R^{15}$, C_{1-6}alkyl substituted with —S(═O)$_2$—C_{1-6}alkyl, C_{1-6}alkyl substituted with —S(═O)$_2$-haloC_{1-6}alkyl, C_{1-6}alkyl substituted with —S(═O)$_2$—$NR^{14}R^{15}$, C_{1-6}alkyl substituted with —NH—S(═O)$_2$—C_{1-6}alkyl, C_{1-6}alkyl substituted with —NH—S(═O)$_2$-haloC_{1-6}alkyl, C_{1-6}alkyl substituted with —NR^{12}—S(═O)$_2$—$NR^{14}R^{15}$, R^6, C_{1-6}alkyl substituted with R^6, C_{1-6}alkyl substituted with —C(═O)—R^6, hydroxyC_{1-6}alkyl substituted with R^6, C_{1-6}alkyl substituted with —Si$(CH_3)_3$, C_{1-6}alkyl substituted with —P(═O)$(OH)_2$ or C_{1-6}alkyl substituted with —P(═O)$(OC_{1-6}alkyl)_2$.

In one embodiment, E represents a bond, C_{2-4}alkenediyl optionally substituted with R^{22}, —CO—$(CR^{22}R^{23})_s$—, —$(CR^{22}R^{23})_s$—O—, —NR^{22}—$(CR^{22}R^{23})_s$—, —$(CR^{22}R^{23})_s$—NR^{22}—, —O—$(CR^{22}R^{23})_s$—, —$(CR^{22}R^{23})_s$—CO—NR^{22}—$(CR^{22}R^{23})_s$— or —$(CR^{22}R^{23})_s$—NR^{22}—CO—$(CR^{22}R^{23})_s$—.

In one embodiment, E represents a bond, C_{2-4}alkenediyl, —CO—$(CR^{22}R^{23})_s$—, —$(CR^{22}R^{23})_s$—CO—, —NR^{22}—$(CR^{22}R^{23})_s$—, —$(CR^{22}R^{23})_s$—NR^{22}—, —$(CR^{22}R^{23})_s$—CO—NR^{22}—$(CR^{22}R^{23})_s$— or —$(CR^{22}R^{23})_s$—NR^{22}—CO—$(CR^{22}R^{23})_s$—.

In one embodiment, E represents C_{2-4}alkenediyl, —CO—$(CR^{22}R^{23})_s$—, —$(CR^{22}R^{23})_s$—O—, —NR^{22}—$(CR^{22}R^{23})_s$—, —$(CR^{22}R^{23})_s$—NR^{22}—, —$(CR^{22}R^{23})_s$—CO—NR^{22}—$(CR^{22}R^{23})_s$— or —$(CR^{22}R^{23})_s$—NR^{22}—CO—$(CR^{22}R^{23})_s$—.

In one embodiment, E represents a bond.

In one embodiment, W is —N(R^3)—.

In one embodiment, W is —C($R^{3a}R^{3b}$)—.

In one embodiment, Y represents -E-D, wherein E is other than a bond.

In one embodiment, Y represents -E-D, wherein E is other than a bond and D represents any one of the following:

- a 3 to 12 ring membered monocyclic or bicyclic carbocyclyl or a 3 to 12 ring membered monocyclic or bicyclic heterocyclyl containing at least one heteroatom selected from N, O or S, wherein said carbocyclyl and heterocyclyl may each be optionally substituted by one or more (e.g. 1, 2 or 3) R^1 groups;
- a 5 to 12 ring membered monocyclic or bicyclic carbocyclyl or a 5 to 12 ring membered monocyclic or bicyclic heterocyclyl containing at least one heteroatom selected from N, O or S, wherein said carbocyclyl and heterocyclyl may each be optionally substituted by one or more (e.g. 1, 2 or 3) R^1 groups;

phenyl or naphthyl, wherein said phenyl or naphthyl may each be optionally substituted by one or more (e.g. 1, 2 or 3) R^1 groups;

a 5 to 12 ring membered monocyclic or bicyclic heterocyclyl containing at least one heteroatom selected from N, O or S, wherein said heterocyclyl may each be optionally substituted by one or more (e.g. 1, 2 or 3) R^1 groups;

a 5 or 6 ring membered monocyclic heterocyclyl containing at least one heteroatom selected from N, O or S, wherein said heterocyclyl may each be optionally substituted by one or more (e.g. 1, 2 or 3) R^1 groups;

a 5 ring membered monocyclic heterocyclyl containing at least one heteroatom selected from N, O or S, wherein said heterocyclyl may each be optionally substituted by one or more (e.g. 1, 2 or 3) R^1 groups;

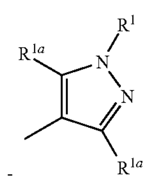
a 5 ring membered monocyclic aromatic heterocyclyl containing at least one heteroatom selected from N, O or S, wherein said heterocyclyl group may each be optionally substituted by one or more (e.g. 1, 2 or 3) R^1 groups;

a 6 ring membered monocyclic heterocyclyl containing at least one heteroatom selected from N, O or S, wherein said heterocyclyl may each be optionally substituted by one or more (e.g. 1, 2 or 3) R^1 groups;

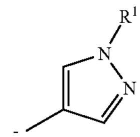
a 6 ring membered monocyclic aromatic heterocyclyl containing at least one heteroatom selected from N, O or S, wherein said heterocyclyl may each be optionally substituted by one or more (e.g. 1, 2 or 3) R^1 groups;

a 12 ring membered bicyclic heterocyclyl containing at least one heteroatom selected from N, O or S, wherein said heterocyclyl may each be optionally substituted by one or more (e.g. 1, 2 or 3) R^1 groups;

a 12 ring membered bicyclic aromatic heterocyclyl containing at least one heteroatom selected from N, O or S, wherein said heterocyclyl may each be optionally substituted by one or more (e.g. 1, 2 or 3) R^1 groups;



wherein R^1 represents hydrogen, C_{1-6}alkyl, C_{2-4}alkenyl, hydroxyC_{1-6}alkyl, haloC_{1-6}alkyl, hydroxyhaloC_{1-6}alkyl, cyanoC_{1-4}alkyl, C_{1-6}alkoxyC_{1-6}alkyl wherein each C_{1-6}alkyl may optionally be substituted with one or two hydroxyl groups, C_{1-6}alkyl substituted with —NR^4R^5, C_{1-6}alkyl substituted with —C(═O)—NR^4R^5, —S(═O)$_2$—C_{1-6}alkyl, —S(═O)$_2$-haloC_{1-6}alkyl, —S(═O)$_2$—$NR^{14}R^{15}$, C_{1-6}alkyl substituted with —S(═O)$_2$—C_{1-6}alkyl, C_{1-6}alkyl substituted with —S(═O)$_2$-haloC_{1-6}alkyl, C_{1-6}alkyl substituted with —S(═O)$_2$—$NR^{14}R^{15}$, C_{1-6}alkyl substituted with —NH—S(═O)$_2$—C_{1-6}alkyl, C_{1-6}alkyl substituted with —NH—S(═O)$_2$-haloC_{1-6}alkyl, C_{1-6}alkyl substituted with —NR^{12}—S(═O)$_2$—$NR^{14}R^{15}$, R^6, C_{1-6}alkyl substituted with R^6, C_{1-6}alkyl substituted with —C(═O)—R^6, hydroxyC_{1-6}alkyl substituted with R^6, C_{1-6}alkyl substituted with —Si(CH_3)$_3$, C_{1-6}alkyl substituted with —P(═O)(OH)$_2$ or C_{1-6}alkyl substituted with —P(═O)(OC_{1-6}alkyl)$_2$; and each R^{1a} is independently selected from hydrogen, C_{1-4}alkyl, hydroxyC_{1-4}alkyl, C_{1-4}alkyl substituted with amino or mono- or di(C_{1-4}alkyl)amino or —NH(C_{3-8}cycloalkyl), cyanoC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, and C_{1-4}alkyl substituted with one or more fluoro atoms;



wherein R^1 represents hydrogen, C_{1-6}alkyl, C_{2-4}alkenyl, hydroxyC_{1-6}alkyl, haloC_{1-6}alkyl, hydroxyhaloC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkyl wherein each C_{1-6}alkyl may optionally be substituted with one or two hydroxyl groups, C_{1-6}alkyl substituted with —NR^4R^5, C_{1-6}alkyl substituted with —C(═O)—NR^4R^5, —S(═O)$_2$—C_{1-6}alkyl, —S(═O)$_2$-haloC_{1-6}alkyl, —S(═O)$_2$—$NR^{14}R^{15}$, C_{1-6}alkyl substituted with —S(═O)$_2$—C_{1-6}alkyl, C_{1-6}alkyl substituted with —S(═O)$_2$-haloC_{1-6}alkyl, C_{1-6}alkyl substituted with —S(═O)$_2$—$NR^{14}R^{15}$, C_{1-6}alkyl substituted with —NH—S(═O)$_2$—C_{1-6}alkyl, C_{1-6}alkyl substituted with —NH—S(═O)$_2$-haloC_{1-6}alkyl, C_{1-6}alkyl substituted with —NR^{12}—S(═O)$_2$—$NR^{14}R^{15}$, R^6, C_{1-6}alkyl substituted with R^6, C_{1-6}alkyl substituted with —C(═O)—R^6, hydroxyC_{1-6}alkyl substituted with R^6, C_{1-6}alkyl substituted with —Si(CH_3)$_3$, C_{1-6}alkyl substituted with —P(═O)(OH)$_2$ or C_{1-6}alkyl substituted with —P(═O)(OC_{1-6}alkyl)$_2$.

In one embodiment, D is other than pyrazolyl, in particular D is piperidinyl, pyridinyl, phenyl, pyrolyl, imidazolyl, triazolyl, pyrolopyridinyl, 1,3-benzodioxolyl, indolyl, thiazolyl, cyclopentyl, azetidinyl, morpholinyl, tetrazolyl, oxazolyl, piperazinyl, 1,2,3,6-tetrahydropyridinyl, 2,5-dihydropyrolyl, pyrimidinyl, pyrrolidinyl, thiadiazolyl, oxadiazolyl, said rings being optionally substituted. Said optional substituents may represent halo, cyano, C_{1-6}alkyl, C_{1-6}alkoxy, —C(═O)—O—C_{1-6}alkyl, hydroxyC_{1-6}alkyl, —NR^4R^5, C_{1-6}alkyl substituted with O—C(═O)—C_{1-6}alkyl, C_{1-6}alkyl substituted with —NR^4R^5, —C(═O)—NR^4R^5, —C(═O)—C_{1-6}alkyl-NR^4R^5, R^6, C_{1-6}alkyl substituted with R^6.

In one embodiment, E is other than a bond and D is other than pyrazolyl, in particular D is piperidinyl, pyridinyl, phenyl, pyrrolyl, imidazolyl, triazolyl, pyrrolopyridinyl, 1,3-benzodioxolyl, indolyl, thiazolyl, cyclopentyl, azetidinyl, morpholinyl, tetrazolyl, oxazolyl, piperazinyl, 1,2,3,6-tetrahydropyridinyl, 2,5-dihydropyrolyl, pyrimidinyl, pyrrolidinyl, thiadiazolyl, oxadiazolyl, said rings being optionally substituted.

In one embodiment, E is a bond and D is optionally substituted 4-pyrazolyl. In one embodiment, E is a bond and D is 4-pyrazolyl substituted at the 1 position with C_{1-6}alkyl for example methyl.

In one embodiment, E is a bond and D is 1-pyrazolyl or 2-pyrazolyl, both may optionally be substituted.

In one embodiment, E is other than a bond and D is 1-pyrazolyl or 2-pyrazolyl, both may optionally be substituted.

In one embodiment, E is other than a bond and D is optionally substituted pyrazolyl.

In one embodiment, E is a bond and D is optionally substituted pyrazolyl.

In one embodiment, E is a bond and D is other than pyrazolyl, in particular D is piperidinyl, pyridinyl, phenyl, pyrolyl, imidazolyl, triazolyl, pyrolopyridinyl, 1,3-benzodioxolyl, indolyl, thiazolyl, cyclopentyl, azetidinyl, morpholinyl, tetrazolyl, oxazolyl, piperazinyl, 1,2,3,6-tetrahydropyridinyl, 2,5-dihydropyrolyl, pyrimidinyl, pyrrolidinyl, said rings being optionally substituted.

In one embodiment, E is a other than a bond and D is other than pyrazolyl, in particular D is piperidinyl, pyridinyl, phenyl, pyrolyl, imidazolyl, triazolyl, pyrolopyridinyl, 1,3-benzodioxolyl, indolyl, thiazolyl, cyclopentyl, azetidinyl, morpholinyl, tetrazolyl, oxazolyl, piperazinyl, 1,2,3,6-tetrahydropyridinyl, 2,5-dihydropyrolyl, pyrimidinyl, pyrrolidinyl, said rings being optionally substituted.

In one embodiment, E is a bond and D is an optionally substituted 6 membered carbocycle, for example phenyl.

In one embodiment, E is a bond and D is an optionally substituted 6 membered heterocycle, for example pyridyl.

In one embodiment, E is a bond and D is an optionally substituted 6 membered partially saturated heterocycle, for example 1,2,3,6-tetrahydropyridyl.

In one embodiment, E is a bond and D is an optionally substituted 6 membered saturated heterocycle, for morpholinyl or piperidinyl. Optional substituents are C(═O)—O—C_{1-6}alkyl.

In one embodiment, E is a bond and D is an optionally substituted aromatic 6 membered heterocycle, for example pyridyl.

In one embodiment, E is a bond and D is an optionally substituted 5 membered heterocycle.

In one embodiment, E is a bond and D is an optionally substituted aromatic 5 membered heterocycle, for example pyrrolyl or pyrazolyl. Optional substituents are C_{1-6}alkyl.

In one embodiment R^1 represents hydrogen, C_{1-6}alkyl, C_{2-4}alkenyl, hydroxyC_{1-6}alkyl, haloC_{1-6}alkyl, hydroxyhaloC_{1-6}alkyl, cyanoC_{1-4}alkyl, C_{1-6}alkoxyC_{1-6}alkyl wherein each C_{1-6}alkyl may optionally be substituted with one or two hydroxyl groups, C_{1-6}alkyl substituted with —NR^4R^5, C_{1-6}alkyl substituted with —C(═O)—NR^4R^5, —S(═O)$_2$—C_{1-6}alkyl, —S(═O)$_2$-haloC_{1-6}alkyl, —S(═O)$_2$—$NR^{14}R^{15}$, C_{1-6}alkyl substituted with —S(═O)$_2$—C_{1-6}alkyl, C_{1-6}alkyl substituted with —S(═O)$_2$-haloC_{1-6}alkyl, C_{1-6}alkyl substituted with —S(═O)$_2$—$NR^{14}R^{15}$, C_{1-6}alkyl substituted with —NH—S(═O)$_2$—C_{1-6}alkyl, C_{1-6}alkyl substituted with —NH—S(═O)$_2$-haloC_{1-6}alkyl, C_{1-6}alkyl substituted with —NR^{12}—S(═O)$_2$—$NR^{14}R^{15}$, R^6, C_{1-6}alkyl substituted with R^6, C_{1-6}alkyl substituted with —C(═O)—R^6, hydroxyC_{1-6}alkyl substituted with R^6, C_{1-6}alkyl substituted with —Si$(CH_3)_3$, C_{1-6}alkyl substituted with —P(═O)$(OH)_2$ or C_{1-6}alkyl substituted with —P(═O)$(OC_{1-6}alkyl)_2$.

In one embodiment R^1 represents hydrogen, C_{1-6}alkyl, C_{2-4}alkenyl, hydroxyC_{1-6}alkyl, haloC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkyl wherein each C_{1-6}alkyl may optionally be substituted with one or two hydroxyl groups, C_{1-6}alkyl substituted with —NR^4R^5, C_{1-6}alkyl substituted with —C(═O)—NR^4R^5, —S(═O)$_2$—C_{1-6}alkyl, —S(═O)$_2$—$NR^{14}R^{15}$, C_{1-6}alkyl substituted with —S(═O)$_2$—C_{1-6}alkyl, C_{1-6}alkyl substituted with —NH—S(═O)$_2$—C_{1-6}alkyl, R^6, C_{1-6}alkyl substituted with R^6, C_{1-6}alkyl substituted with —C(═O)—R^6, hydroxyC_{1-6}alkyl substituted with R^6, or C_{1-6}alkyl substituted with —Si$(CH_3)_3$.

In one embodiment, R^1 represents hydrogen, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, C_{1-6}alkyl substituted with —S(═O)$_2$—C_{1-6}alkyl or R^6.

In one embodiment, R^1 represents hydrogen, C_{1-6}alkyl, —C(═O)—O—C_{1-6}alkyl, hydroxyC_{1-6}alkyl, C_{1-6}alkyl substituted with —S(═O)$_2$—C_{1-6}alkyl or R^6.

In one embodiment R^6 represents optionally substituted 4 to 7-membered monocyclic heterocyclyl containing at least one heteroatom selected from N, O or S. In one embodiment R^6 represents optionally substituted non-aromatic 4 to 7-membered (e.g. 6 membered) monocyclic heterocyclyl containing at least one heteroatom selected from N, O or S. In one embodiment R^6 represents tetrahydropyranyl.

In one embodiment, R^1 represents hydrogen, C_{1-6}alkyl (e.g methyl), hydroxyC_{1-6}alkyl (e.g. CH_2CH_2OH), C_{1-6}alkyl substituted with —S(═O)$_2$—C_{1-6}alkyl (e.g. CH_2CH_2—SO_2—CH_3) or optionally substituted non-aromatic 4 to 7-membered (e.g. 6 membered) monocyclic heterocyclyl containing at least one heteroatom selected from N, O or S (e.g. tetrahydropyranyl).

In one embodiment, R1 represents —C(═O)—O—C_{1-6}alkyl (e.g. C(═O)—O—C$(CH_3)_3$).

In one embodiment R^1 represents hydrogen.

In one embodiment R^1 represents C_{1-6}alkyl. In one embodiment R^1 represents methyl.

In one embodiment each R^2 is independently selected from hydroxyl, halogen, cyano, C_{1-4}alkyl, C_{2-4}alkenyl, C_{1-4}alkoxy, hydroxyC_{1-4}alkyl, hydroxyC_{1-4}alkoxy, haloC_{1-4}alkyl, haloC_{1-4}alkoxy, C_{1-4}alkoxyC_{1-4}alkyl, R^{13}, C_{1-4}alkoxy substituted with R^{13}, —C(═O)—R^{13}, C_{1-4}alkyl substituted with NR^7R^8, C_{1-4}alkoxy substituted with NR^7R^8, —NR^7R^8 and —C(═O)—NR^7R^8; or when two R^2 groups are attached to adjacent carbon atoms they may be taken together to form a radical of formula —O—$(C(R^{17})_2)_p$—O— wherein R^{17} represents hydrogen or fluorine and p represents 1 or 2.

In one embodiment each R^2 is independently selected from hydroxyl, halogen, cyano, C_{1-4}alkyl, C_{2-4}alkenyl, C_{1-4}alkoxy, hydroxyC_{1-4}alkyl, hydroxyC_{1-4}alkoxy, haloC_{1-4}alkoxy, C_{1-4}alkoxyC_{1-4}alkyl, R^{13}, C_{1-4}alkoxy substituted with R^{13}, —C(═O)—R^{13}, C_{1-4}alkyl substituted with NR^7R^8, C_{1-4}alkoxy substituted with NR^7R^8, —NR^7R^8 or —C(═O)—NR^7R^8.

In one embodiment one or more R^2 represents C_{1-4}alkoxy, for example CH_3O—, or halo, for example fluoro or chloro, in particular fluoro.

In one embodiment one or more R^2 represents C_{1-4}alkoxy, for example CH_3O—.

In one embodiment n is equal to 0. In one embodiment n is equal to 1. In one embodiment n is equal to 2. In one embodiment n is equal to 3. In one embodiment n is equal to 4.

In one embodiment, n is equal to 2, 3 or 4.

In one embodiment n is equal to 2 and one R^2 is present at the 3-position and the other is present at the 5-position.

In one embodiment n is equal to 2 and one R^2 is present at the 3-position and the other is present at the 5-position and each R^2 represents C_{1-4}alkoxy, for example each R^2 represents CH_3O—.

In one embodiment n is equal to 3 and one R^2 is present at the 2-position, one R^2 is present at the 3-position and one R^2 is present at the 5-position.

In one embodiment n is equal to 3 and one R^2 is present at the 3-position and represents C_{1-4}alkoxy, for example CH_3O—; one R^2 is present at the 5-position and represents C_{1-4}alkoxy, for example CH_3O—; one R^2 is present at the 2-position and represents halogen, for example fluoro or chloro, in particular fluoro.

In one embodiment n is equal to 4 and one R^2 is present at the 2-position, one R^2 is present at the 3-position, one R^2 is present at the 5-position and one R^2 is present at the 6-position.

In one embodiment n is equal to 4 and one R^2 is present at the 3-position and represents C_{1-4}alkoxy, for example CH_3O—; one R^2 is present at the 5-position and represents C_{1-4}alkoxy, for example CH_3O—; one R^2 is present at the

2-position and represents halogen, for example fluoro, and one R^2 is present at the 6-position and represents halogen, for example fluoro.

In one embodiment, R^3 represents C_{1-6}alkyl, hydroxyC_{1-6}alkyl, hydroxyhaloC_{1-6}alkyl, hydroxyC_{2-6}alkynyl, haloC_{1-6}alkyl optionally substituted (e.g. substituted) with —O—C(═O)—C_{1-6}alkyl, C_{1-6}alkyl substituted with —C(═O)—C_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkyl wherein each C_{1-6}alkyl may optionally be substituted with one or two hydroxyl groups, C_{1-6}alkoxyC_{1-6}alkyl wherein each C_{1-6}alkyl may optionally be substituted with one or two hydroxyl groups or with —O—C(═O)—C_{1-6}alkyl, C_{1-6}alkyl substituted with R^9, C_{1-6}alkyl substituted with —$NR^{10}R^{11}$, C_{1-6}alkyl substituted with hydroxyl and —$NR^{10}R^{11}$, C_{1-6}alkyl substituted with one or two halogens and —$NR^{10}R^{11}$, C_{1-6}alkyl substituted with —C(═O)—O—C_{1-6}alkyl, C_{1-6}alkyl substituted with —C(═O)—$NR^{10}R^{11}$, C_{1-6}alkyl substituted with carboxyl, C_{1-6}alkyl substituted with —O—C(═O)—$NR^{10}R^{11}$, C_{1-6}alkyl substituted with —NR^{12}—S(═O)$_2$—C_{1-6}alkyl, C_{1-6}alkyl substituted with —NR^{12}—S(═O)$_2$—$NR^{14}R^{15}$, C_{1-6}alkyl substituted with R^9 and optionally substituted with —O—C(═O)—C_{1-6}alkyl, C_{1-6}alkyl substituted with hydroxyl and R^9, —C_{1-6}alkyl-C(R^{12})═N—O—R^{12}, —S(═O)$_2$—$NR^{14}R^{15}$, C_{1-6}alkyl substituted with —S(═O)$_2$—C_{1-6}alkyl, C_{1-6}alkyl substituted with —C(═O)—$NR^{10}R^{11}$, C_{1-6}alkyl substituted with —C(═O)—R^9, C_{2-6}alkenyl substituted with R^9, C_{2-6}alkynyl substituted with R^9, hydroxyC_{1-6}alkoxy, C_{2-6}alkenyl, C_{2-6}alkynyl, R^{13}, C_{1-6}alkyl substituted with C_{1-6}alkoxyC_{1-6}alkyl-C(═O)— or C_{1-6}alkyl substituted with —P(═O)(OC_{1-6}alkyl)$_2$.

In one embodiment R^3 represents C_{1-6}alkyl, hydroxyC_{1-6}alkyl, hydroxyhaloC_{1-6}alkyl, haloC_{1-6}alkyl, C_{1-6}alkyl substituted with —C(═O)—C_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkyl wherein each C_{1-6}alkyl may optionally be substituted with one or two hydroxyl groups, C_{1-6}alkyl substituted with R^9, C_{1-6}alkyl substituted with —$NR^{10}R^{11}$, C_{1-6}alkyl substituted with hydroxyl and —$NR^{10}R^{11}$, C_{1-6}alkyl substituted with one or two halogens and —$NR^{10}R^{11}$, C_{1-6}alkyl substituted with —C(═O)—O—C_{1-6}alkyl, C_{1-6}alkyl substituted with —C(═O)—$NR^{10}R^{11}$, C_{1-6}alkyl substituted with carboxyl, C_{1-6}alkyl substituted with —O—C(═O)—$NR^{10}R^{11}$, C_{1-6}alkyl substituted with —NR^{12}—S(═O)$_2$—C_{1-6}alkyl, C_{1-6}alkyl substituted with —NR^{12}—S(═O)$_2$—$NR^{14}R^{15}$, C_{1-6}alkyl substituted with hydroxyl and R^9, —C_{1-6}alkyl-C(R^{12})═N—O—R^{12}, C_{1-6}alkyl substituted with —C(═O)—$NR^{10}R^{11}$, C_{1-6}alkyl substituted with —C(═O)—R^9, C_{2-6}alkynyl substituted with R^9, hydroxyC_{1-6}alkoxy, C_{2-6}alkenyl, C_{2-6}alkynyl, R^{13} or C_{1-6}alkyl substituted with C_{1-6}alkoxyC_{1-6}alkyl-C(═O)—.

In one embodiment R^3 represents C_{1-6}alkyl, hydroxyC_{1-6}alkyl, haloC_{1-6}alkyl, haloC_{1-6}alkyl optionally substituted with —O—C(═O)—C_{1-6}alkyl, hydroxyhaloC_{1-6}alkyl, hydroxyC_{2-6}alkynyl, C_{1-6}alkyl substituted with —C(═O)—C_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkyl wherein each C_{1-6}alkyl may optionally be substituted with one or two hydroxyl groups or with —O—C(═O)—C_{1-6}alkyl, C_{1-6}alkyl substituted with R^9, cyanoC_{1-6}alkyl, C_{1-6}alkyl substituted with —$NR^{10}R^{11}$, C_{1-6}alkyl substituted with hydroxyl and —$NR^{10}R^{11}$, C_{1-6}alkyl substituted with one or two halo atoms and —$NR^{10}R^{11}$. C_{1-6}alkyl substituted with —C(═O)—O—C_{1-6}alkyl, C_{1-6}alkyl substituted with C_{1-6}alkoxyC_{1-6}alkyl-C(═O)—, C_{1-6}alkyl substituted with —C(═O)—$NR^{10}R^{11}$, C_{1-6}alkyl substituted with —C(═O)—$NR^{14}R^{15}$, C_{1-6}alkyl substituted with carboxyl, C_{1-6}alkyl substituted with —O—C(═O)—$NR^{10}R^{11}$, C_{1-6}alkyl substituted with —NR^{12}—S(═O)$_2$—C_{1-6}alkyl, C_{1-6}alkyl substituted with —NR^{12}—S(═O)$_2$—$NR^{14}R^{15}$, C_{1-6}alkyl substituted with R^9 and substituted with —O—C(═O)—C_{1-6}alkyl, C_{1-6}alkyl substituted with hydroxyl and R^9, —C_{1-6}alkyl-C(R^{12})═N—O—R^{12}, —S(═O)$_2$—$NR^{14}R^{15}$, C_{1-6}alkyl substituted with —S(═O)$_2$—C_{1-6}alkyl, C_{1-6}alkyl substituted with —C(═O)—R^9, C_{2-6}alkenyl substituted with R^9, C_{2-6}alkynyl substituted with R^9, C_{1-6}alkyloxyC_{1-6}alkyl wherein each C_{1-6}alkyl may optionally be substituted with one or two hydroxyl groups, C_{2-6}alkenyl, C_{2-6}alkynyl, R^{13}, or C_{1-6}alkyl substituted with —P(═O)(OC_{1-6}alkyl)$_2$.

In one embodiment, R^3 represents C_{1-6}alkyl, hydroxyC_{1-6}alkyl, hydroxyhaloC_{1-6}alkyl, haloC_{1-6}alkyl, C_{1-6}alkyl substituted with —C(═O)—C_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkyl wherein each C_{1-6}alkyl may optionally be substituted with one or two hydroxyl groups, C_{1-6}alkyl substituted with R^9, C_{1-6}alkyl substituted with —$NR^{10}R^{11}$, C_{1-6}alkyl substituted with hydroxyl and —$NR^{10}R^{11}$, C_{1-6}alkyl substituted with one or two halogens and —$NR^{10}R^{11}$, C_{1-6}alkyl substituted with —C(═O)—O—C_{1-6}alkyl, C_{1-6}alkyl substituted with —O—C(═O)—$NR^{10}R^{11}$, C_{1-6}alkyl substituted with carboxyl, C_{1-6}alkyl substituted with —NR^{12}—S(═O)$_2$—C_{1-6}alkyl, C_{1-6}alkyl substituted with —NR^{12}—S(═O)$_2$—$NR^{14}R^{15}$, C_{1-6}alkyl substituted with hydroxyl and R^9, —C_{1-6}alkyl-C(R^{12})═N—O—R^{12}, C_{1-6}alkyl substituted with —C(═O)—$NR^{10}R^{11}$, C_{1-6}alkyl substituted with —C(═O)—R^9, C_{2-6}alkynyl substituted with R^9, hydroxyC_{1-6}alkoxy, C_{2-6}alkenyl, C_{2-6}alkynyl or R^{13}.

In one embodiment R^3 represents hydroxyC_{1-6}alkyl, hydroxyhaloC_{1-6}alkyl, C_{1-6}alkyl substituted with R^9, C_{1-6}alkyl substituted with —$NR^{10}R^{11}$, C_{2-6}alkynyl substituted with R^9, or C_{2-6}alkynyl.

In one embodiment R^3 represents C_{2-6}alkynyl, haloC_{1-6}alkyl optionally substituted with —O—C(═O)—C_{1-6}alkyl, hydroxyC_{1-6}alkyl optionally substituted with —O—C(═O)—C_{1-6}alkyl, hydroxyhaloC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkyl wherein each C_{1-6}alkyl may optionally be substituted with one or two hydroxyl groups or with —O—C(═O)—C_{1-6}alkyl, C_{1-6}alkyl substituted with R^9, C_{2-6}alkynyl substituted with R^9, C_{1-6}alkyl substituted with —$NR^{10}R^{11}$, or C_{1-6}alkyl substituted with —O—C(═O)—$NR^{10}R^{11}$.

In one embodiment R^3 represents hydroxyC_{1-6}alkyl, hydroxyhaloC_{1-6}alkyl, C_{1-6}alkyl substituted with R^9, C_{1-6}alkyl substituted with —$NR^{10}R^{11}$, C_{1-6}alkoxyC_{1-6}alkyl wherein each C_{1-6}alkyl may optionally be substituted with one or two hydroxyl groups or with —O—C(═O)—C_{1-6}alkyl, C_{2-6}alkynyl substituted with R^9, or C_{2-6}alkynyl.

In one embodiment R^3 represents hydroxyC_{1-6}alkyl, hydroxyhaloC_{1-6}alkyl, C_{1-6}alkyl substituted with R^9, C_{1-6}alkyl substituted with —$NR^{10}R^{11}$, C_{2-6}alkynyl substituted with R^9, or C_{2-6}alkynyl.

In one embodiment R^3 represents hydroxyC_{1-6}alkyl, haloC_{1-6}alkyl, C_{1-6}alkyl substituted with R^9, C_{1-6}alkyl substituted with —$NR^{10}R^{11}$, C_{1-6}alkoxyC_{1-6}alkyl, or C_{2-6}alkynyl.

In one embodiment R^3 represents hydroxyC_{1-6}alkyl, hydroxyhaloC_{1-6}alkyl, C_{1-6}alkyl substituted with R^9, C_{1-6}alkyl substituted with —$NR^{10}R^{11}$, C_{2-6}alkynyl substituted with R^9, or C_{2-6}alkynyl.

In one embodiment R^3 represents C_{2-6}alkynyl. R^3 may represent —CH_2—C≡C—H.

In one embodiment R^3 represents C_{2-6}alkynyl (e.g. —CH_2—C≡C—) substituted with R^9. R^9 may represent an optionally substituted aromatic 6-membered monocyclic heterocycle containing one or two nitrogen heteroatoms, for example pyridinyl or pyrimidinyl. The heterocyclyl may be substituted, for example substituted with one C_{1-4}alkoxyl substituent, for example —OCH_3. R^3 may represent

—CH_2—C≡C— (2-pyridinyl), or —CH_2—C≡C— (2-pyrimidinyl). Or R^9 may represent an optionally substituted aromatic 5-membered monocyclic heterocycle containing one or two nitrogen heteroatoms, for example imidazolyl. The heterocycle may be substituted, for example substituted with C_{1-4}alkyl, for example methyl. R^3 may represent —CH_2—C≡C— (imidazol-2-yl substituted with methyl in position 1).

In one embodiment when R^3 represents C_{1-6}alkyl (e.g. C_{1-4}alkyl) substituted with R^9. R^9 represents an optionally substituted saturated or an aromatic 5 or 6 membered monocyclic heterocyclyl, for example optionally substituted isoxazolidinyl, pyrimidinyl, imidazolyl or pyrrolidinyl.

In one embodiment when R^3 represents C_{1-6}alkyl (e.g. C_{1-4}alkyl) substituted with R^9, wherein R^9 represents an optionally substituted aromatic 6 membered monocyclic heterocyclyl containing one or two nitrogen heteroatom, for example pyrimidinyl or pyridinyl.

In one embodiment when R^3 represents C_{1-6}alkyl (e.g. methyl or n-propyl) substituted with R^9, wherein R^9 represents unsubstituted isoxazolidinyl, unsubstituted pyrimidinyl, unsubstituted imidazolyl (e.g. imidazol-2-yl), imidazolyl (e.g. imidazol-2-yl) substituted with —$S(O)_2$—N$(CH_3)_2$, oxo-substituted pyrrolidinyl or pyrrolidinyl substituted by 3-methoxy-pyrimidin-2-yl.

In one embodiment R^3 represents C_{1-6}alkyl substituted with hydroxyl, halo and/or —$NR^{10}R^{11}$. In one embodiment R^3 represents C_{1-6}alkyl substituted with hydroxyl, halo or —$NR^{10}R^{11}$, wherein the C_{1-6}alkyl group is a straight chain alkyl group e.g. 2-ethyl, n-propyl, n-butyl. In a further embodiment R^3 represents C_{1-6}alkyl substituted with hydroxyl or —$NR^{10}R^{11}$.

In one embodiment R^3 represents hydroxyC_{1-6}alkyl. R^3 may represent —CH_2CH_2OH or —$CH_2CH_2CH_2OH$.

In one embodiment R^3 represents hydroxyhaloC_{1-6}alkyl, for example R^3 may represent —$CH_2CHOHCF_3$.

In one embodiment R^3 represents C_{1-6}alkyl substituted with —$NR^{10}R^{11}$.

In one embodiment R^3 represents C_{1-4}alkyl substituted with —$NR^{10}R^{11}$. In one embodiment R^3 represents C_{1-4}alkyl substituted —$NR^{10}R^{11}$, wherein the C_{1-4}alkyl group is a straight chain alkyl group e.g. 2-ethyl, n-propyl. In one embodiment R^3 represents C_{1-4}alkyl substituted with —$NR^{10}R^{11}$, wherein the C_{1-4}alkyl group is an ethylene group (—CH_2CH_2—).

In one embodiment when R^3 represents C_{1-6}alkyl (e.g. 2-ethyl, n-propyl) substituted with —$NR^{10}R^{11}$, wherein R^{10} and R^{11} are independently selected from hydrogen, C_{1-6}alkyl and haloC_{1-6}alkyl (e.g. hydrogen, iso-propyl or —CH_2CF_3).

In one embodiment when R^3 represents C_{1-6}alkyl substituted with —$NR^{10}R^{11}$, R^{10} and R^{11} have the following meanings:

a) each of R^{10} and R^{11} represent hydrogen. R^3 may represent $CH_2CH_2CH_2NH_2$;

b) one of R^{10} and R^{11} represents hydrogen and the other represents C_{1-6}alkyl, for example —$CH(CH_3)_2$. R^3 may represent $CH_2CH_2NHCH(CH_3)_2$; or

c) one of R^{10} and R^{11} represents hydrogen and the other represents haloC_{1-6}alkyl, for example —CH_2CF_3. R^3 may represent $CH_2CH_2CH_2NHCH_2CF_3$;

In one embodiment R^3 represents —$CH_2CH_2NHCH(CH_3)_2$.

R^{3a} may represent —$NR^{10}R^{11}$, hydroxyl, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, hydroxyhaloC_{1-6}alkyl, haloC_{1-6}alkyl, C_{1-6}alkyl substituted with —C(═O)—C_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkyl wherein each C_{1-6}alkyl may optionally be substituted with one or two hydroxyl groups, C_{1-6}alkyl substituted with R^9, C_{1-6}alkyl substituted with —$NR^{10}R^{11}$, C_{1-6}alkyl substituted with hydroxyl and —$NR^{10}R^{11}$, C_{1-6}alkyl substituted with one or two halogens and —$NR^{10}R^{11}$, C_{1-6}alkyl substituted with —C(═O)—O—C_{1-6}alkyl, C_{1-6}alkyl substituted with —O—C(═O)—$NR^{10}R^{11}$, C_{1-6}alkyl substituted with carboxyl, C_{1-6}alkyl substituted with O—C(═O)—$NR^{10}R^{11}$, C_{1-6}alkyl substituted with —NR^{12}—S(═O)$_2$—C_{1-6}alkyl, C_{1-6}alkyl substituted with —NR^{12}—S(═O)$_2$—$NR^{14}R^{15}$, C_{1-6}alkyl substituted with hydroxyl and R^9, —C_{1-6}alkyl-C(R^{12})═N—O—R^{12}, C_{1-6}alkyl substituted with —C(═O)—$NR^{10}R^{11}$, C_{1-6}alkyl substituted with —C(═O)—R^9, C_{2-6}alkynyl substituted with R^9, hydroxyC_{1-6}alkoxy, C_{2-6}alkenyl, C_{2-6}alkynyl, R^{13} or C_{1-6}alkyl substituted with C_{1-6}alkoxyC_{1-6}alkyl-C(═O)—.

In one embodiment R^{3a} is —$NR^{10}R^{11}$, hydroxyl, hydroxyC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkyl substituted with —C(═O)—C_{1-6}alkyl, C_{1-6}alkyl substituted with —C(═O)—O—C_{1-6}alkyl, C_{1-6}alkyl substituted with R^9, C_{1-6}alkyl substituted with —$NR^{10}R^{11}$, C_{1-6}alkyl substituted with hydroxyl and —$NR^{10}R^{11}$, or C_{1-6}alkyl substituted with —C(═O)—$NR^{10}R^{11}$.

In one embodiment R^{3a} represents hydroxyl, C_{1-6}alkyl substituted with —C(═O)—$NR^{10}R^{11}$ cyanoC_{1-6}alkyl, hydroxyC_{1-6}alkyl, C_{1-6}alkyl substituted with —C(═O)—O—C_{1-6}alkyl.

In one embodiment R^{3a} represents C_{1-6}alkyl substituted with —C(═O)—$NR^{10}R^{11}$. In one embodiment R^{3a} represents C_{1-4}alkyl substituted —C(═O)—$NR^{10}R^{11}$, wherein the C_{1-4}alkyl group is a straight chain alkyl group e.g. methyl. In one embodiment, R^{3a} represents C_{1-6}alkyl substituted with —C(═O)—$NR^{10}R^{11}$, wherein R^{10} and R^{11} represent hydrogen.

In one embodiment, R^{3a} represents cyanoC_{1-6}alkyl, for example R^{3a} represents —CH_2—CN.

In one embodiment, R^{3a} represents C_{1-6}alkyl substituted with —C(═O)—O—C_{1-6}alkyl, for example R^{3a} represents —CH_2—$COOCH_3$ or —CH_2—$COOCH_2CH_3$.

In one embodiment, R^{3a} represents hydroxyC_{1-6}alkyl, for example —CH_2—CH_2—OH.

In one embodiment R^{3a} represents hydroxyl.

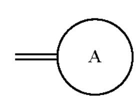
In one embodiment R^{3b} represents hydrogen.

In one embodiment R^{3b} represents hydroxyl.

In one embodiment R^{3a} represents hydroxyl and R^{3b} represents hydrogen.

In one embodiment R^{3a} represents hydroxyl, C_{1-6}alkyl substituted with —C(═O)—$NR^{10}R^{11}$, cyanoC_{1-6}alkyl, hydroxyC_{1-6}alkyl, or C_{1-6}alkyl substituted with —C(═O)—O—C_{1-6}alkyl and R^{3b} represents hydrogen.

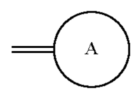
In one embodiment R^{3a} and R^{3b} are taken together to form ═O, to form ═NR^{10}, to form cyclopropyl together with the carbon atom to which they are attached, to form ═CH—C_{0-4}alkyl substituted with R^{3c}, or to form



wherein ring A is a monocyclic 5 to 7 membered saturated heterocycle containing one heteroatom selected from N, O or S, said heteroatom not being positioned in alpha position of the double bond, wherein ring A is optionally being substituted with cyano, C_{1-4}alkyl, hydroxyC_{1-4}alkyl, H_2N—C_{1-4}alkyl, (C_{1-4}alkyl)NH—C_{1-4}alkyl, (C_{1-4}alkyl)$_2$N—

C_{1-4}alkyl, (haloC_{1-4}alkyl)NH—C_{1-4}alkyl, C_{1-4}alkoxy-C_{1-4}alkyl, —C(═O)—NH_2, —C(═O)—NH(C_{1-4}alkyl), —C(═O)—N(C_{1-4}alkyl)$_2$.

In one embodiment R^{3a} and R^{3b} are taken together to form ═O, to form cyclopropyl together with the carbon atom to which they are attached, to form ═CH—C_{0-4}alkyl substituted with R^{3c}, or to form



wherein ring A is a monocyclic 5 to 7 membered saturated heterocycle containing one heteroatom selected from N, O or S, said heteroatom not being positioned in alpha position of the double bond.

In one embodiment R^{3a} and R^{3b} are taken together to form ═O.

In one embodiment R^{3a} and R^{3b} are taken together to form cyclopropyl together with the carbon atom to which they are attached.

In one embodiment R^{3a} and R^{3b} are taken together to form ═CH—C_{0-4}alkyl substituted with R^{3c}.

In one embodiment R^{3c} represents hydrogen.

In one embodiment R^{3c} represents cyano.

In one embodiment R^{3c} represents hydroxyl, C_{1-6}alkoxy, R^9, —$NR^{10}R^{11}$, cyano, C(═O)—C_{1-6}alkyl or —CH(OH)—C_{1-6}alkyl.

In one embodiment R^{3c} represents hydroxyl, —$NR^{10}R^{11}$, cyano, or —C(═O)—C_{1-6}alkyl.

In one embodiment R^{3a} and R^{3b} are taken together to form ═CH—C_{0-4}alkyl in the Z configuration.

In one embodiment R^{3a} and R^{3b} are taken together to form ═CH-cyano. In one embodiment, R^{3a} and R^{3b} are taken together to form ═CH-cyano in the Z configuration.

In one embodiment R^{3a} and R^{3b} are taken together to form ═CH-cyano. In one embodiment, R^{3a} and R^{3b} are taken together to form ═CH-cyano in the E configuration.

In one embodiment, R^9 is selected from:

an optionally substituted C_{3-8}cycloalkyl,

an optionally substituted aromatic 5 membered monocyclic heterocyclyl,

an optionally substituted saturated 6 membered monocyclic heterocyclyl,

a saturated or an aromatic 3, 4, 5 or 6 membered monocyclic heterocyclyl containing one or two oxygen heteroatoms,

an optionally substituted 4 membered heterocyclyl containing one oxygen heteroatom,

an optionally substituted aromatic 6 membered monocyclic heterocycle containing one or two nitrogen heteroatoms,

a partially saturated 6 membered monocyclic heterocyclyl containing one nitrogen heteroatom which may optionally be substituted,

an optionally substituted saturated 4 membered monocyclic heterocyclyl containing one nitrogen heteroatom,

a saturated 5 membered monocyclic heterocyclyl containing one nitrogen heteroatom,

a saturated 6 membered monocyclic heterocyclyl containing one nitrogen heteroatom,

a bicyclic heterocyclyl containing a benzene ring fused to a 5- or 6-membered ring containing 1, 2 or 3 ring heteroatoms,

a 4, 5 or 6 membered monocyclic saturated heterocycle substituted with two substituents which are attached to the same atom and which are taken together to form a 4 to 7-membered saturated monocyclic heterocyclyl containing at least one heteroatom selected from N, O or S,

an optionally substituted aromatic 5 membered monocyclic heterocyclyl containing one sulphur heteroatom,

an optionally substituted aromatic 5 membered monocyclic heterocyclyl containing one sulphur and one nitrogen heteroatom,

a saturated 6 membered monocyclic heterocyclyl containing two nitrogen heteroatoms,

an aromatic 5 membered monocyclic heterocyclyl containing four nitrogen heteroatoms,

an aromatic 5 membered monocyclic heterocyclyl containing one oxygen and two nitrogen heteroatoms,

an optionally substituted aromatic 5 membered monocyclic heterocyclyl containing two nitrogen heteroatoms,

an optionally substituted aromatic 5 membered monocyclic heterocyclyl containing three nitrogen heteroatoms,

a saturated 5 membered monocyclic heterocyclyl containing one nitrogen and one oxygen heteroatom,

a saturated 6 membered monocyclic heterocyclyl containing one nitrogen and one sulphur heteroatom,

a saturated 7 membered monocyclic heterocyclyl containing two nitrogen heteroatoms,

a saturated 7 membered monocyclic heterocyclyl containing one nitrogen and one oxygen heteroatom, and

phenyl or naphthyl, in particular phenyl.

In one embodiment, R^9 represents an optionally substituted 5 membered aromatic or saturated heterocycle, such as for example imidazolyl, pyrrolidinyl, isoxazolidinyl. Optional substituents may represent ═O, a 5 or 6-membered aromatic monocyclic heterocyclyl containing at least one heteroatom selected from N, O or S wherein said heterocyclyl is optionally substituted with R^{16}; or —S(═O)$_2$—$NR^{14}R^{15}$.

In one embodiment, R^9 represents an optionally substituted 5 membered aromatic or saturated heterocycle, such as for example imidazolyl, pyrrolidinyl, isoxazolidinyl. Optional substituents may represent ═O, a 5 or 6-membered aromatic monocyclic heterocyclyl containing at least one heteroatom selected from N, O or S wherein said heterocyclyl is optionally substituted with R^{16}; —S(═O)$_2$—$NR^{14}R^{15}$, C_{1-4}alkyl, or C_{1-4}alkyl substituted with —NH—S(═O)$_2$-haloC_{1-4}alkyl.

In one embodiment, R^9 represents C_{3-6}cycloalkyl, such as for example cyclopropyl, a 3 membered saturated heterocyclyl, such as for example oxiranyl, an optionally substituted 5 membered saturated heterocycle, such as for example pyrrolidinonyl, an optionally substituted 6 membered aromatic or saturated heterocycle, such as for example pyridyl, pyrimidinyl, pyrazinyl, piperazinyl, or morpholinyl, an optionally substituted bicyclic heterocycle, such as for example 1H-isoindol-1,3-dione. Optional substituents may represent ═O, C_{1-4}alkoxy, C_{1-4}alkyl substituted with —$NR^{14}R^{15}$, hydroxyC_{1-4}alkyl, or C_{1-4}alkyl-C(═O)—.

In one embodiment, R^9 represents an optionally substituted 5 membered aromatic heterocycle, such as for example imidazolyl, or an optionally substituted 6 membered aromatic heterocycle, such as for example pyridyl, pyrimidinyl or pyrazinyl. Optional substituents may represent C_{1-4}alkoxy or —S(═O)$_2$—$NR^{14}R^{15}$.

In one embodiment, R^9 represents an optionally substituted 5 membered aromatic heterocycle, such as for example imidazolyl. Optional substituents may represent S(═O)$_2$—$NR^{14}R^{15}$.

In one embodiment, R^9 represents an optionally substituted 6 membered aromatic heterocycle, such as for example pyridinyl or pyrimidinyl. Optional substituents may represent C_{1-4}alkoxy.

In one embodiment R^{10} represents hydrogen or C_{1-6}alkyl or haloC_{1-6}alkyl.

In one embodiment R^{10} is hydrogen.

In one embodiment R^{11} represents hydrogen, C_{1-6}alkyl, haloC_{1-6}alkyl, —C(=O)—C_{1-6}alkyl, —S(=O)$_2$—C_{1-6}alkyl, —S(=O)$_2$—$NR^{14}R^{15}$, hydroxyC_{1-6}alkyl, —C(=O)-hydroxyhaloC_{1-6}alkyl, —C(=O)—R^6, cyano-C_{1-6}alkyl, R^6, —C(=O)—R^6, C_{1-6}alkyl substituted with R^6, —C(=O)-haloC_{1-6}alkyl, C_{1-6}alkyl substituted with —Si$(CH_3)_3$, C_{1-6}alkyl substituted with —$NR^{14}R^{15}$, C_{1-6}alkyl substituted with —C(=O)—$NR^{14}R^{15}$, C_{1-6}alkoxy, hydroxyhaloC_{1-6}alkyl, carboxyl, or C_{1-6}alkoxyC_{1-6}alkyl.

In one embodiment R^{10} and R^{11} represent hydrogen or C_{1-6}alkyl.

In one embodiment, R^6 represents a 6-membered monocyclic saturated heterocyclyl which is optionally substituted. For example piperazinyl or morpholinyl or tetrahydropyranyl, optionally substituted with halogen, C_{1-6}alkyl, or C_{1-6}alkyl-O—C(=O)—.

In one embodiment, R^6 represents a 6-membered monocyclic aromatic heterocyclyl which is optionally substituted. For example pyridinyl, optionally substituted with halogen, C_{1-6}alkyl, or C_{1-6}alkyl-O—C(=O)—.

In one embodiment R^6 represents an optionally substituted saturated 4 to 7-membered monocyclic heterocyclyl containing at least one heteroatom selected from N, O or S, such as for example tetrahydropyran.

In one embodiment, R^{12} represents hydrogen or C_{1-4}alkyl optionally substituted with C_{1-4}alkyloxy.

In one embodiment, R^{13} represents a saturated 4 to 6-membered monocyclic heterocyclyl containing at least one heteroatom selected from N or O.

In one embodiment, R^{14} and R^{15} each independently represent hydrogen or C_{1-4}alkyl. In one embodiment, R^{14} and R^{15} each independently represent C_{1-4}alkyl.

In one embodiment, R^{22} and R^{23} each independently represent hydrogen.

In one embodiment, W is —N(R^3)— and Y is D (E is a bond).

In one embodiment, W is —N(R^3)— and Y is -E-D wherein E is other than a bond.

In one embodiment, W is —N(R^3)—, and Y is —CR^{18}=N—OR^{19}.

In one embodiment, W is —N(R^3)—, Y is -E-D, wherein E is a bond and D is a 5 or 6 membered monocyclic aromatic heterocyclyl, wherein said heterocyclyl may optionally be substituted by one or more (e.g. 1, 2 or 3) R^1 groups, in particular D is pyrazolyl optionally substituted with C_{1-6}alkyl, more in particular D is pyrazolyl optionally substituted with C_{1-6}alkyl and n is 2, even more in particular D is pyrazolyl optionally substituted with C_{1-6}alkyl; n is 2, R^2 is C_{1-6}alkyloxy, even further in particular D is pyrazolyl optionally substituted with C_{1-6}alkyl; n is 2, R^2 is C_{1-6}alkyloxy and said R^2 is placed in position 3 and 5.

In one embodiment, W is —N(R^3)—, Y is -E-D, wherein E is a bond and D is piperidinyl, pyridinyl, phenyl, pyrrolyl, imidazolyl, triazolyl, pyrolopyridinyl, 1,3-benzodioxolyl, indolyl, thiazolyl, cyclopentyl, azetidinyl, morpholinyl, tetrazolyl, oxazolyl, piperazinyl, 1,2,3,6-tetrahydropyridinyl, 2,5-dihydropyrrolyl, pyrimidinyl, pyrrolidinyl, thiadiazolyl, oxadiazolyl, said rings being optionally substituted, more in particular D is piperidinyl, pyridinyl, phenyl, pyrrolyl, imidazolyl, triazolyl, pyrolopyridinyl, 1,3-benzodioxolyl, indolyl, thiazolyl, cyclopentyl, azetidinyl, morpholinyl, tetrazolyl, oxazolyl, piperazinyl, 1,2,3,6-tetrahydropyridinyl, 2,5-dihydropyrrolyl, pyrimidinyl, pyrrolidinyl, thiadiazolyl, oxadiazolyl, said rings being optionally substituted and n is 2, even more in particular D is piperidinyl, pyridinyl, phenyl, pyrrolyl, imidazolyl, triazolyl, pyrolopyridinyl, 1,3-benzodioxolyl, indolyl, thiazolyl, cyclopentyl, azetidinyl, morpholinyl, tetrazolyl, oxazolyl, piperazinyl, 1,2,3,6-tetrahydropyridinyl, 2,5-dihydropyrrolyl, pyrimidinyl, pyrrolidinyl, thiadiazolyl, oxadiazolyl, said rings being optionally substituted; n is 2, R^2 is C_{1-6}alkyloxy, even further in particular D is piperidinyl, pyridinyl, phenyl, pyrrolyl, imidazolyl, triazolyl, pyrolopyridinyl, 1,3-benzodioxolyl, indolyl, thiazolyl, cyclopentyl, azetidinyl, morpholinyl, tetrazolyl, oxazolyl, piperazinyl, 1,2,3,6-tetrahydropyridinyl, 2,5-dihydropyrrolyl, pyrimidinyl, pyrrolidinyl, thiadiazolyl, oxadiazolyl, said rings being optionally substituted; n is 2, R^2 is C_{1-6}alkyloxy and said R^2 is placed in position 3 and 5.

In one embodiment, W is —C($R^{3a}R^{3b}$)— and Y is D (E is a bond).

In one embodiment, W is —C($R^{3a}R^{3b}$)— and Y is -E-D wherein E is other than a bond.

In one embodiment, W is —C($R^{3a}R^{3b}$)—, and Y is —CR^{18}=N—OR^{19}.

In one embodiment, W is —C($R^{3a}R^{3b}$)—, Y is -E-D, wherein E is a bond and D is a 5 or 6 membered monocyclic aromatic heterocyclyl, wherein said heterocyclyl may optionally be substituted by one or more (e.g. 1, 2 or 3) R^1 groups, in particular D is pyrazolyl optionally substituted with C_{1-6}alkyl, more in particular D is pyrazolyl optionally substituted with C_{1-6}alkyl and n is 2, even more in particular D is pyrazolyl optionally substituted with C_{1-6}alkyl; n is 2, R^2 is C_{1-6}alkyloxy, even further in particular D is pyrazolyl optionally substituted with C_{1-6}alkyl; n is 2, R^2 is C_{1-6}alkyloxy and said R^2 is placed in position 3 and 5.

In one embodiment, W is —C($R^{3a}R^{3b}$)—, Y is -E-D, wherein E is a bond and D is piperidinyl, pyridinyl, phenyl, pyrrolyl, imidazolyl, triazolyl, pyrolopyridinyl, 1,3-benzodioxolyl, indolyl, thiazolyl, cyclopentyl, azetidinyl, morpholinyl, tetrazolyl, oxazolyl, piperazinyl, 1,2,3,6-tetrahydropyridinyl, 2,5-dihydropyrrolyl, pyrimidinyl, pyrrolidinyl, thiadiazolyl, oxadiazolyl, said rings being optionally substituted, more in particular D is piperidinyl, pyridinyl, phenyl, pyrrolyl, imidazolyl, triazolyl, pyrolopyridinyl, 1,3-benzodioxolyl, indolyl, thiazolyl, cyclopentyl, azetidinyl, morpholinyl, tetrazolyl, oxazolyl, piperazinyl, 1,2,3,6-tetrahydropyridinyl, 2,5-dihydropyrrolyl, pyrimidinyl, pyrrolidinyl, thiadiazolyl, oxadiazolyl, said rings being optionally substituted and n is 2, even more in particular D is piperidinyl, pyridinyl, phenyl, pyrrolyl, imidazolyl, triazolyl, pyrolopyridinyl, 1,3-benzodioxolyl, indolyl, thiazolyl, cyclopentyl, azetidinyl, morpholinyl, tetrazolyl, oxazolyl, piperazinyl, 1,2,3,6-tetrahydropyridinyl, 2,5-dihydropyrrolyl, pyrimidinyl, pyrrolidinyl, thiadiazolyl, oxadiazolyl, said rings being optionally substituted; n is 2, R^2 is C_{1-6}alkyloxy, even further in particular D is piperidinyl, pyridinyl, phenyl, pyrrolyl, imidazolyl, triazolyl, pyrolopyridinyl, 1,3-benzodioxolyl, indolyl, thiazolyl, cyclopentyl, azetidinyl, morpholinyl, tetrazolyl, oxazolyl, piperazinyl, 1,2,3,6-tetrahydropyridinyl, 2,5-dihydropyrrolyl, pyrimidinyl, pyrrolidinyl, thiadiazolyl, oxadiazolyl, said rings being optionally substituted; n is 2, R^2 is C_{1-6}alkyloxy and said R^2 is placed in position 3 and 5.

In one embodiment, n represents an integer equal to 2, 3 or 4; R^2 represents C_{1-4}alkoxy or halogen, for example CH_3O— or fluoro; R^3 represents hydroxyC_{1-6}alkyl, hydroxyhaloC_{1-6}alkyl, C_{1-6}alkyl substituted with R^9,

C_{1-6}alkyl substituted with C_{2-6}alkynyl substituted with R^9 or C_{2-6}alkynyl; Y is -E-D wherein E represents a bond, D represents pyrazolyl, in particular pyrazol-4-yl, optionally substituted with C_{1-6}alkyl. hydroxyC_{1-6}alkyl, C_{1-6}alkyl substituted with —S(═O)$_2$—C_{1-6}alkyl or R^6; W is —N(R^3)— or —C($R^{3a}R^{3b}$)— wherein R^{3a} is hydroxyl, R^{3b} is hydrogen.

In one embodiment, n represents an integer equal to 2, 3 or 4; R^2 represents C_{1-4}alkoxy or halogen, for example CH_3O— or fluoro or chloro; R^3 represents hydroxy-C_{1-6}alkyl, hydroxyhaloC_{1-6}alkyl, C_{1-6}alkyl substituted with R^9, C_{1-6}alkyl substituted with —$NR^{10}R^{11}$, C_{2-6}alkynyl substituted with R^9 or C_{2-6}alkynyl; R^{3a} represents hydroxyl, C_{1-6}alkyl substituted with —C(═O)—$NR^{10}R^{11}$, cyano-C_{1-6}alkyl, hydroxyC_{1-6}alkyl, C_{1-6}alkyl substituted with C(═O)—O—C_{1-6}alkyl; R^{3b} represents hydrogen; or R^{3a} and R^{3b} are taken together to form ═O or to form ═CH—C_{0-4}alkyl substituted with R^{3c}; Y is -E-D wherein E represents a bond, D represents an optionally substituted 5 membered heterocycle, an optionally substituted 6 membered heterocycle or phenyl, in particular an optionally substituted aromatic 5 membered heterocycle, an optionally substituted saturated, partially saturated or aromatic 6 membered heterocycle or phenyl, in particular pyrazol-4-yl, optionally substituted with C_{1-6}alkyl. hydroxyC_{1-6}alkyl, C_{1-6}alkyl substituted with —S(═O)$_2$—C_{1-6}alkyl or R^6, or phenyl, or pyridyl or morpholinyl or 1,2,3,6-tetrahydropyridyl or pyrrolyl optionally substituted with C_{1-6}alkyl.

In one embodiment, n represents an integer equal to 2, 3 or 4; R^2 represents C_{1-4}alkoxy or halogen, for example CH_3O— or fluoro or chloro; R^3 represents hydroxy-C_{1-6}alkyl, hydroxyhaloC_{1-6}alkyl, C_{1-6}alkyl substituted with R^9, C_{1-6}alkyl substituted with —$NR^{10}R^{11}$, C_{2-6}alkynyl substituted with R^9 or C_{2-6}alkynyl; R^{3a} represents hydroxyl, C_{1-6}alkyl substituted with —C(═O)—$NR^{10}R^{11}$, cyano-C_{1-6}alkyl, hydroxyC_{1-6}alkyl, C_{1-6}alkyl substituted with —C(═O)—O—C_{1-6}alkyl; R^{3b} represents hydrogen; or R^{3a} and R^{3b} are taken together to form ═O or to form ═CH—C_{0-4}alkyl substituted with R^{3c}; R^{3c} represents cyano; Y is -E-D wherein E represents a bond, D represents an optionally substituted 5 membered heterocycle, an optionally substituted 6 membered heterocycle or phenyl, in particular an optionally substituted aromatic 5 membered heterocycle, an optionally substituted saturated, partially saturated or aromatic 6 membered heterocycle or phenyl, in particular pyrazol-4-yl, optionally substituted with C_{1-6}alkyl. hydroxyC_{1-6}alkyl, C_{1-6}alkyl substituted with —S(═O)$_2$—C_{1-6}alkyl or R^6, or phenyl, or pyridyl or morpholinyl or 1,2,3,6-tetrahydropyridyl or pyrrolyl optionally substituted with C_{1-6}alkyl; W is —N(R^3)— or —C($R^{3a}R^{3b}$)—; R^9 represents an optionally substituted 5 membered aromatic or saturated heterocycle, such as for example imidazolyl, pyrrolidinyl, isoxazolidinyl, said heterocycles being optionally substituted with ═O, —S(═O)$_2$—$NR^{14}R^{15}$, C_{1-4}alkyl, C_{1-4}alkyl substituted with —NH—S(═O)$_2$-haloC_{1-4}alkyl, or a 5 or 6-membered aromatic monocyclic heterocyclyl containing at least one heteroatom selected from N, O or S wherein said heterocyclyl, for example pyrimidinyl, is optionally substituted with R^{16}; or R^9 represents an optionally substituted 6 membered aromatic heterocycle, such as for example pyridinyl or pyrimidinyl, said heterocycles being optionally substituted with C_{1-4}alkoxy; R^{16} represents C_{1-4}alkoxy; R^{10} and R^{11} each independently represent hydrogen or C_{1-6}alkyl; R^{14} and R^{15} each independently represent hydrogen or C_{1-4}alkyl.

In one embodiment there is provided compounds of formula (I) including any tautomeric or stereochemically isomeric form thereof, wherein

W is —N(R^3)— or —C($R^{3a}R^{3b}$)—;

each R^2 is independently selected from halogen, for example fluoro or chloro, or C_{1-4}alkoxy, for example —OCH_3;

Y represents -E-D;

E represents a bond;

D represents a 3 to 12 ring membered monocyclic or bicyclic carbocyclyl or a 3 to 12 ring membered monocyclic or bicyclic heterocyclyl containing at least one heteroatom selected from N, O or S, for example pyrazolyl, phenyl, pyridyl, morpholinyl, 1,2,3,6-tetrahydropyridyl, pyrrolyl, piperidinyl, wherein said carbocyclyl and heterocyclyl may each be optionally substituted by one or more (e.g. 1, 2 or 3) R^1 groups; R^1 represents hydrogen, C_{1-6}alkyl, for example —CH_3, hydroxyC_{1-6}alkyl, for example _CH_2CH_2OH, C_{1-6}alkyl substituted with —S(═O)$_2$—C_{1-6}alkyl, for example —CH_2CH_2—S(═O)$_2$—CH_3, R^6; for example tetrahydropyran-2-yl, or —C(═O)—O—C_{1-6}alkyl;

R^{3a} represents hydroxyl; or R^{3a} represents hydroxyl, C_{1-6}alkyl substituted with —C(═O)—$NR^{10}R^{11}$, cyano-C_{1-6}alkyl, hydroxyC_{1-6}alkyl, C_{1-6}alkyl substituted with —C(═O)—O—C_{1-6}alkyl;

R^{3b} represents hydrogen; or

R^{3a} and R^{3b} are taken together to form ═O or to form ═CH—C_{0-4}alkyl substituted with cyano,

R^3 represents

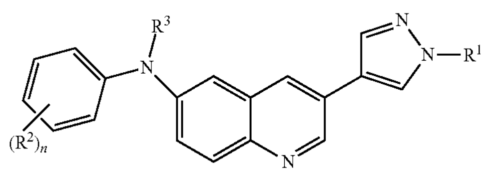
- hydroxyC_{1-6}alkyl, for example —CH_2CH_2OH, —$CH_2CH_2CH_2OH$,
- hydroxyhaloC_{1-6}alkyl, for example —CH_2CHOH—CF_3,
- C_{1-6}alkyl substituted with R^9, for example
  - methyl substituted with pyriminidin-2-yl,
  - methyl substituted with imidazol-2-yl optionally substituted with —S(═O)$_2$—N(CH_3)$_2$ for example in the 3 position,
  - propyl substituted with pyrrolidin-1-yl substituted in the 2 position by ═O or —CH_2—NH—SO_2—CF_3,
  - propyl substituted with isoxazolin-2-yl,
  - pyrrolidin-4-yl substituted in the 1 position by pyrimidin-2-yl substituted in the 4 position by —OCH_3,
  - methyl substituted with pyrrolidin-5-yl substituted in the 2 position by ═O,
- C_{1-6}alkyl substituted with —$NR^{10}R^{11}$, for example —$CH_2CH_2NHCH(CH_3)_2$, —$CH_2CH_2CH_2NHCH_2CF_3$, —$CH_2CH_2NHCH_3$,
- C_{2-6}alkynyl substituted with R^9, for example
  - —CH_2—C(triple bond)C— substituted with pyridin-2-yl substituted in the 3 position with —OCH_3
  - —CH_2—C(triple bond)C— substituted with imidazol-2-yl substituted in the 1 position with —CH_3
  - —CH_2—C(triple bond)C— substituted with pyrimidin-2-yl substituted in the 4 position with —OCH_3, or
- C_{2-6}alkynyl; for example —CH_2—C≡C—H; and

n independently represents an integer equal to 2, 3 or 4;

the N-oxides thereof, the pharmaceutically acceptable salts thereof or the solvates thereof.

In one embodiment the compound of formula (I) is a compound of formula (Ia) including any tautomeric or stereochemically isomeric form thereof:

(Ia)



wherein n, R^1, R^2 and R^3 are as defined herein;
the N-oxides thereof, the pharmaceutically acceptable salts thereof or the solvates thereof.

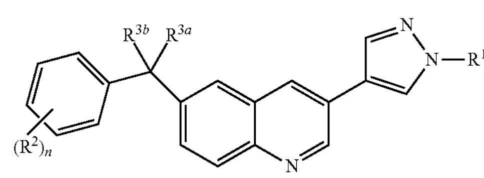
A compound of formula (Ia) including any tautomeric or stereochemically isomeric form thereof wherein:
R^1 represents hydrogen, C_{1-6}alkyl (e.g methyl), —C(═O)—O—C_{1-6}alkyl (e.g. —C(═O)—O—$C(CH_3)_3$), hydroxyC_{1-6}alkyl, C_{1-6}alkyl substituted with —S(═O)$_2$—C_{1-6}alkyl or optionally substituted non-aromatic 4 to 7-membered (e.g. 6 membered) monocyclic heterocyclyl containing at least one heteroatom selected from N, O or S (e.g. tetrahydropyranyl);
R^2 represents C_{1-4}alkoxy, for example CH_3O—, or halo, for example fluoro or chloro;
n=2; or n=2, 3 or 4; and
R^3 represents hydroxyC_{1-6}alkyl, hydroxyhaloC_{1-6}alkyl, C_{1-6}alkyl substituted with R^9, C_{1-6}alkyl substituted with —$NR^{10}R^{11}$, C_{2-6}alkynyl substituted with R^9, or C_{2-6}alkynyl;
the N-oxides thereof, the pharmaceutically acceptable salts thereof or the solvates thereof.

A compound of formula (Ia) including any tautomeric or stereochemically isomeric form thereof wherein
R^1 represents hydrogen, C_{1-6}alkyl (e.g methyl), hydroxyC_{1-6}alkyl (e.g. —CH_2CH_2OH), C_{1-6}alkyl substituted with —S(═O)$_2$—C_{1-6}alkyl (e.g. —CH_2CH_2—SO_2—CH_3) or optionally substituted non-aromatic 4 to 7-membered (e.g. 6 membered) monocyclic heterocyclyl containing at least one heteroatom selected from N, O or S (e.g. tetrahydropyran);
R^2 represents C_{1-4}alkoxy, for example CH_3O—, or halo, for example fluoro or chloro;
n=2; or n=2, 3 or 4; and
R^3 represents
(i) hydroxyC_{1-6}alkyl, R^3 may represent —CH_2CH_2OH or —$CH_2CH_2CH_2OH$;
(ii) hydroxyhaloC_{1-6}alkyl, for example —$CH_2CHOHCF_3$;
(iii) C_{1-6}alkyl (e.g. 2-ethyl, n-propyl) substituted with —$NR^{10}R^{11}$, wherein R^{10} and R^{11} are independently selected from hydrogen, C_{1-6}alkyl and haloC_{1-6}alkyl (e.g. hydrogen, iso-propyl or —CH_2CF_3);
(iv) C_{1-6}alkyl (e.g. methyl or n-propyl) substituted with R^9, wherein R^9 represents optionally substituted saturated or an aromatic 5 or 6 membered monocyclic heterocyclyl (e.g. unsubstituted isoxazolidinyl, unsubstituted pyrimidinyl, unsubstituted imidazolyl, imidazolyl substituted with —S(O)$_2$—N$(CH_3)_2$, oxo-substituted pyrrolidinyl, pyrrolidinyl substituted by 3-methoxy-pyrimidin-2-yl), or pyrrolidinyl substituted with —CH_2—NH—SO_2—CF_3;
(v) C_{2-6}alkynyl (e.g. —CH_2—C≡C—H); or
(vi) C_{2-6}alkynyl (e.g. —CH_2—C≡C—) substituted with R^9, wherein R^9 may represent an optionally substituted aromatic 5 or 6-membered monocyclic heterocycle containing one or two nitrogen heteroatoms, for example pyridinyl or pyrimidinyl or imidazolyl (e.g. —CH_2—C≡C— (2-pyridinyl), or —CH_2—C≡C— (2-pyrimidinyl)) substituted, for example substituted with one C_{1-4}alkoxyl substituent, for example —OCH_3, or —CH_2—C≡C— (2-imidazolyl) which may be substituted for example with methyl,
the N-oxides thereof, the pharmaceutically acceptable salts thereof or the solvates thereof.

A compound of formula (Ia) including any tautomeric or stereochemically isomeric form thereof wherein
R^1 represents hydrogen, C_{1-6}alkyl (e.g methyl), hydroxyC_{1-6}alkyl (e.g. —CH_2CH_2OH), C_{1-6}alkyl substituted with —S(═O)$_2$—C_{1-6}alkyl (e.g. —CH_2CH_2—SO_2—CH_3) or optionally substituted non-aromatic 4 to 7-membered (e.g. 6 membered) monocyclic heterocyclyl containing at least one heteroatom selected from N, O or S (e.g. tetrahydropyran);
R^2 represents C_{1-4}alkoxy, for example CH_3O—, or halo, for example fluoro or chloro;
n=2; or n=2, 3 or 4; and
R^3 represents
(i) hydroxyC_{1-6}alkyl, R^3 may represent —CH_2CH_2OH or —$CH_2CH_2CH_2OH$;
(ii) hydroxyhaloC_{1-6}alkyl, for example —$CH_2CHOHCF_3$;
(iii) C_{1-6}alkyl (e.g. 2-ethyl, n-propyl) substituted with —$NR^{10}R^{11}$, wherein R^{10} and R^{11} are independently selected from hydrogen, C_{1-6}alkyl and haloC_{1-6}alkyl (e.g. hydrogen, iso-propyl or —CH_2CF_3);
(iv) C_{1-6}alkyl (e.g. methyl or n-propyl) substituted with R^9, wherein R^9 represents optionally substituted saturated or an aromatic 5 or 6 membered monocyclic heterocyclyl (e.g. unsubstituted isoxazolidinyl, unsubstituted pyrimidinyl, unsubstituted imidazolyl, imidazolyl substituted with —S(O)$_2$—N$(CH_3)_2$, oxo-substituted pyrrolidinyl, pyrrolidinyl substituted by 3-methoxy-pyrimidin-2-yl), or pyrrolidinyl substituted with —CH_2—NH—SO_2—CF_3;
(v) C_{2-6}alkynyl (e.g. —CH_2C≡C—H); or
(vi) C_{2-6}alkynyl (e.g. —CH_2—C≡C—) substituted with R^9, wherein R^9 may represent an optionally substituted aromatic 5 or 6-membered monocyclic heterocycle containing one or two nitrogen heteroatoms, for example pyridinyl or pyrimidinyl or imidazolyl (e.g. —CH_2—C≡C— (2-pyridinyl), or —CH_2—C≡C— (2-pyrimidinyl)) substituted, for example substituted with one C_{1-4}alkoxyl substituent, for example —OCH_3, or —CH_2—C≡C— (2-imidazolyl) which may be substituted for example with methyl,
the N-oxides thereof, the pharmaceutically acceptable salts thereof or the solvates thereof.

In one embodiment the compound of formula (I) is a compound of formula (Ib) including any tautomeric or stereochemically isomeric form thereof:

(Ib)



wherein n, R^1, R^2, R^{3a} and R^{3b} are as defined herein;
the N-oxides thereof, the pharmaceutically acceptable salts thereof or the solvates thereof.

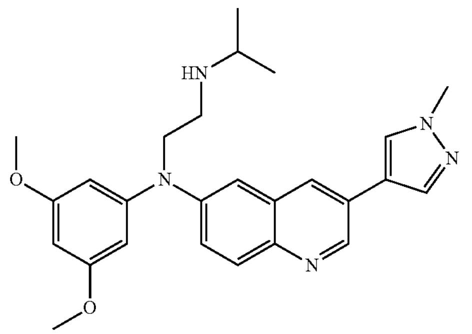
A compound of formula (Ib) including any tautomeric or stereochemically isomeric form thereof wherein:
R^1 represents C_{1-6}alkyl (e.g methyl);
R^2 represents C_{1-4}alkoxy, for example CH_3O—, or halo, for example fluoro or chloro;
n=2, 3 or 4; and
R^{3a} represents hydroxyl, C_{1-6}alkyl substituted with —C(═O)—$NR^{11}R^{11}$, cyanoC_{1-6}alkyl, hydroxyC_{1-6}alkyl,

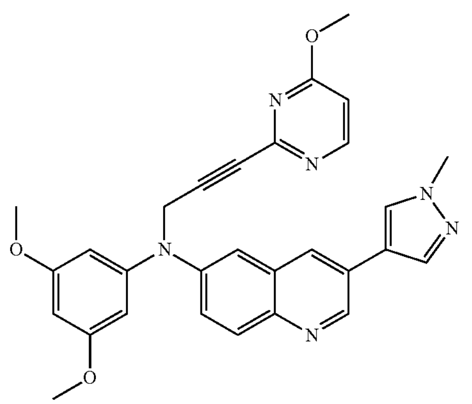
C_{1-6}alkyl substituted with —C(═O)—O—C_{1-6}alkyl; R^{3b} represents hydrogen; or R^{3a} and R^{3b} are taken together to form ═O or to form ═CH—C_{0-4}alkyl substituted with R^{3c};

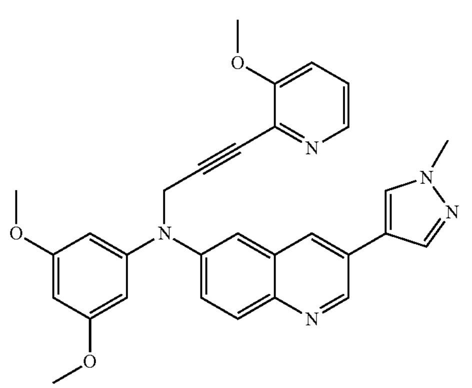
R^{3c} represents cyano;

the N-oxides thereof, the pharmaceutically acceptable salts thereof or the solvates thereof.

In one embodiment, the compound of formula (I) is any one of the following compounds

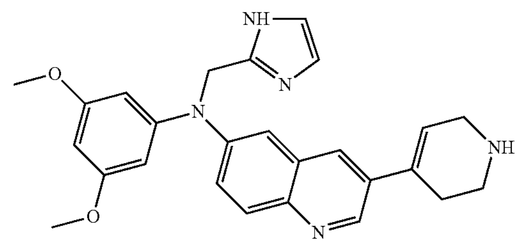


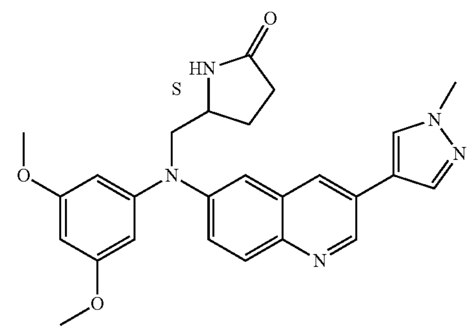


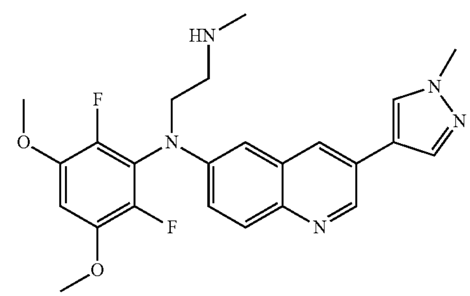


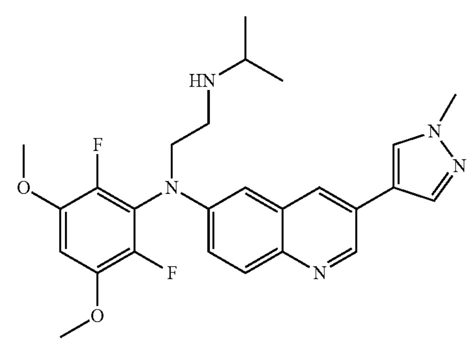
a N-oxide thereof, a pharmaceutically acceptable salt thereof or a solvate thereof.

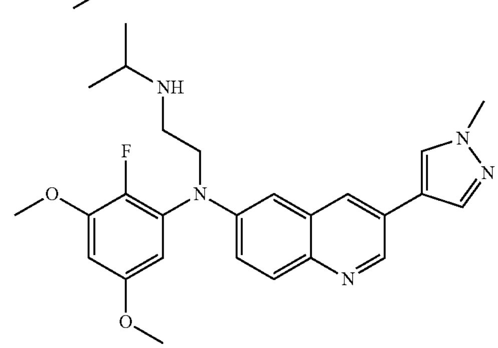
In one embodiment, the compound of formula (I) is any one of the following compounds











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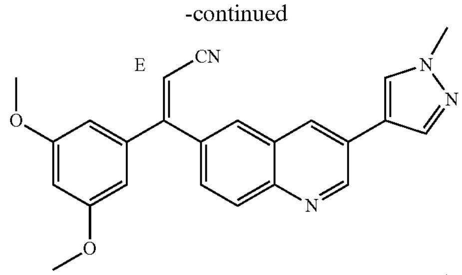
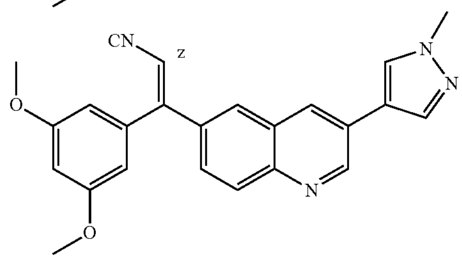




a N-oxide thereof, a pharmaceutically acceptable salt thereof or a solvate thereof.

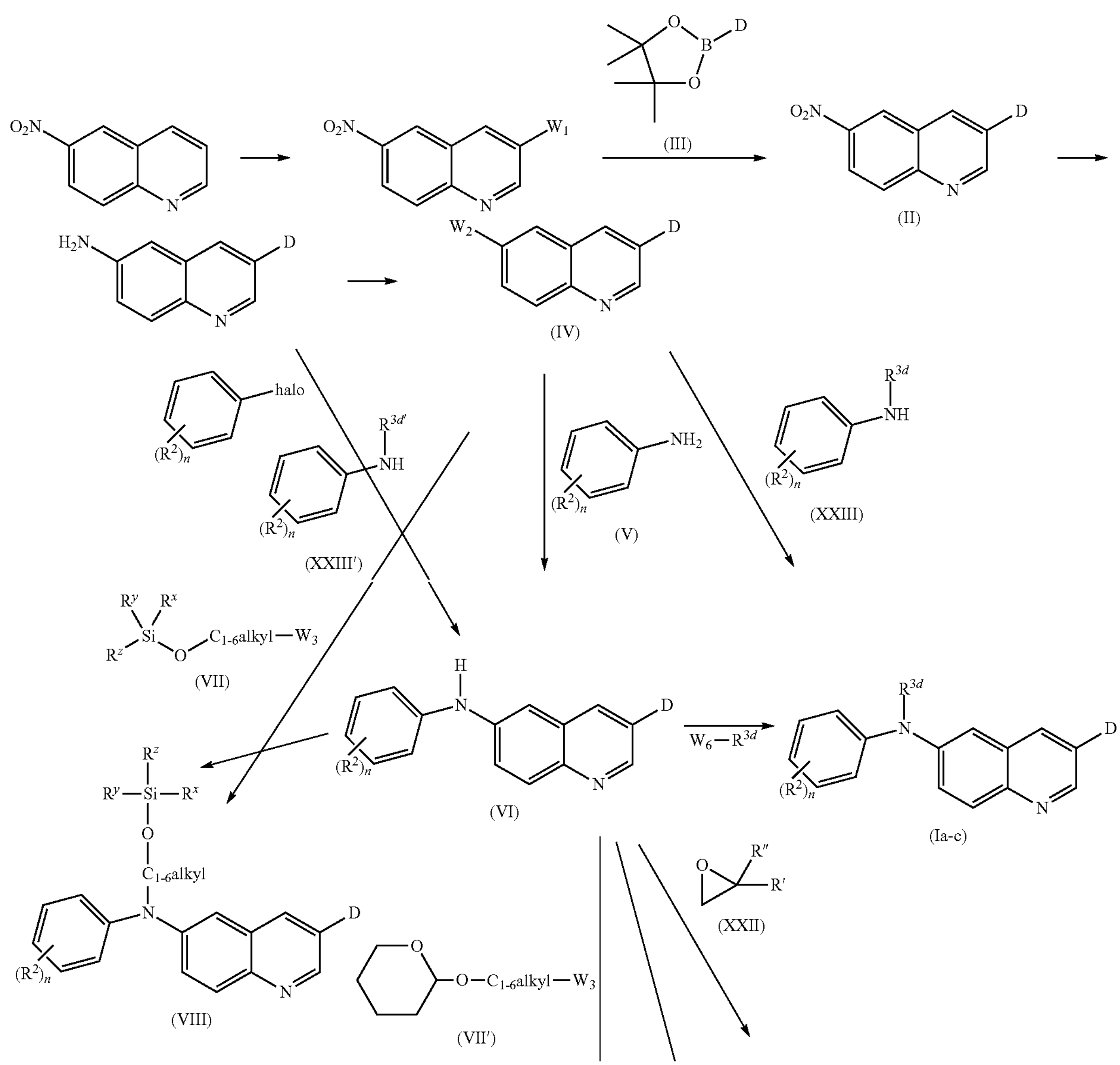
For the avoidance of doubt, it is to be understood that each general and specific preference, embodiment and example for one substituent may be combined, whenever possible, with each general and specific preference, embodiment and example for one or more, preferably, all other substituents as defined herein and that all such embodiments are embraced by this application.

Methods for the Preparation of Compounds of Formula (I)

In this section, as in all other sections of this application unless the context indicates otherwise, references to formula (I) also include all other sub-groups and examples thereof as defined herein.

In general, compounds of formula (I) wherein W is —N(R^3)— and Y is D (E is a bond), said compounds being represented by formula (Ia), can be prepared according to the following reaction Scheme 1.

Scheme 1



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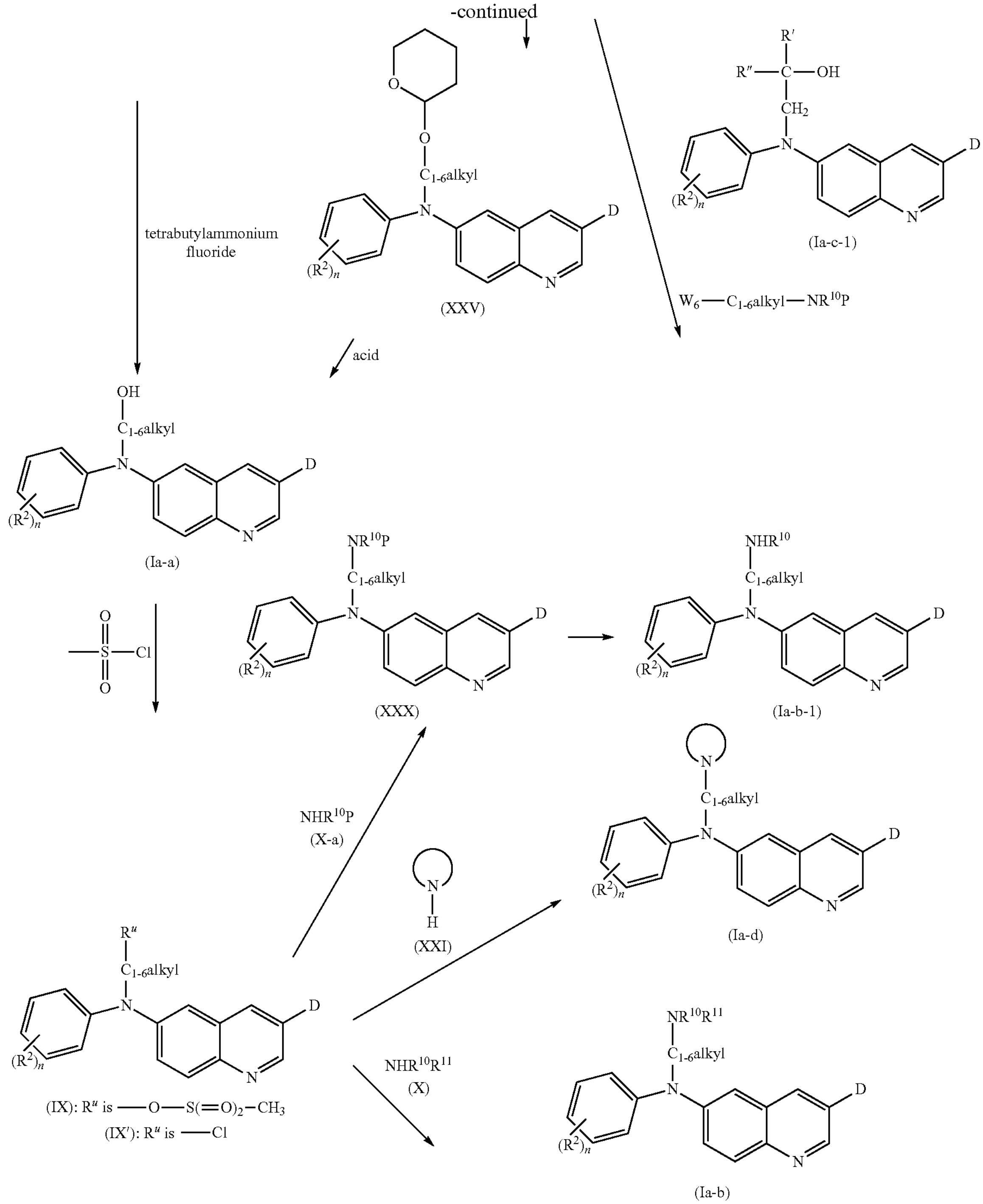


In scheme 1, a 6-nitro quinoline is halogenated, preferably brominated, on carbon C-3. The resulting intermediate wherein W_1 represent a suitable leaving group, such as for example halo, e.g. bromo and the like, is then reacted with an intermediate of formula (III) to prepare an intermediate of formula (II) in the presence of a suitable catalyst, such as for example tetrakis(triphenylphosphine)palladium (0) or palladium (II) acetate or $Pd(Ph_3)_2Cl_2$ or $PdCl_2$ (dppf), a suitable base, such as for example sodium carbonate or cesium carbonate, a suitable ligand, such as for example triphenylphosphine or xantphos, and a suitable solvent or solvent mixture, such as for example ethylene glycol dimethylether and water or dioxane and water. An intermediate of formula (II) can also be prepared by reacting the halogenated nitroquinoline with D in the presence of a suitable catalyst, such as for example Pd_2 dba_3, a suitable ligand, such as for example xantphos, a suitable base, such as for example cesium carbonate, and a suitable solvent, such as for example dioxane. An intermediate of formula (II) is then reduced into a 6-aminoquinoline derivative by art-known methods (hydrogenation in the presence of a suitable catalyst, such as for example Raney Nickel or Pd on carbon, and a suitable solvent, such as for example an alcohol, e.g. methanol, or tetrahydrofuran, or mixtures thereof). This type of reaction can also be performed in the presence of ammonium chloride, iron, and a suitable solvent, such as for example a mixture of tetrahydrofuran, water and methanol. Such derivative can then be converted into an intermediate of formula (IV) wherein W_2 represent a suitable leaving group such as for example halo, e.g. bromo or iodo, by art-known diazotation methods. The 6-aminoquinoline derivative can also react with a halophenyl derivative, such as a bromo or iodo phenyl derivative, in the presence of a suitable catalyst, such as for example tris(dibenzylideneacetone) dipalladium(0), a suitable base, such as Cs_2CO_3, a suitable ligand, such as for example 2-dicyclohexylphosphino-2',4',6'-tri-1-propyl-1,1'-biphenyl or xantphos in a suitable solvent or solvent mixture, such as for example 2-methyl-2-propanol to result in an intermediate of formula (VI).

The intermediate of formula (IV) can react with an intermediate of formula (V) in the presence of a suitable catalyst, such as for example palladium (II) acetate, a suitable base, such as sodium tert-butoxide or Cs_2CO_3, a suitable ligand, such as for example 1, 1'-[1,1'-binaphthalene]-2,2'-diylbis[1,1-diphenylphosphine], and a suitable solvent or solvent mixture, such as for example dioxane or ethylene glycol dimethylether and water, resulting in an intermediate of formula (VI). Said intermediate of formula (VI) can then be reacted with an intermediate of formula (VII) wherein W_3 represents a suitable leaving group, such as for example halo, e.g. bromo and wherein R^x and R^y represent C_{1-4}alkyl, and R^z represent C_{1-4}alkyl or phenyl, for instance R^x and R^y represent CH_3 and R^z represents $C(CH_3)_3$ or phenyl, in the presence of a suitable base, such as for example sodium hydride, and a suitable solvent, such as for example N,N-dimethylformamide or N,N-dimethylacetamide, resulting in an intermediate of formula (VIII). Intermediates of formula (VIII) or intermediates of formula (VIII) wherein the R^1 substituent carries a suitable protective group can also be prepared by reacting an intermediate of formula (IV) or an intermediate of formula (IV) wherein the R^1 substituent carries a suitable protective group with an intermediate of formula (XXIII') wherein $R^{3d'}$ represent —C_{1-6}alkyl-O—Si(R^x)(R^y)(R^z) in the presence of a suitable catalyst, such as for example palladium (II) acetate, a suitable ligand, such as for example racemic-2,2'-bis(diphenylphosphino)-1,1'-binaphtyl, a suitable base, such as for example Cs_2CO_3, and a suitable solvent, such as for example 1,2-dimethoxyethane. Intermediates of formula (VIII) can be converted into a compound of formula (I) wherein R^3 represents —C_{1-6}alkyl-OH, said compounds being represented by formula (Ia-a) or compounds of formula (I-a) wherein the R^1 substituent carries a suitable protective group, by reaction with tetrabutylammonium fluoride in the presence of a suitable solvent, such as for example tetrahydrofuran. This type of reaction can also be performed in the presence of a suitable acid, such as for example acetic acid or HCl, and a suitable solvent, such as for example tetrahydrofurane or dioxane. Alternatively, an intermediate of formula (VI) can react with an intermediate of formula (VII') wherein W_3 represents a suitable leaving group, such as for example halo, e.g. bromo and the like, in the presence of a suitable base, such as for example sodium hydride, and a suitable solvent, such as for example N,N-dimethylformamide or N,N-dimethylacetamide, resulting in an intermediate of formula (XXV) which can then be deprotected in the presence of a suitable acid, such as for example HCl, and a suitable solvent, such as for example an alcohol, e.g. methanol or isopropanol, to give a compound of formula (Ia-a). The compounds of formula (Ia-a) or compounds of formula (Ia-a) wherein the R^1 substituent carries a suitable protective group can be reacted with methanesulfonyl chloride in the presence of a suitable base, such as for example triethylamine, diisopropylethanamine or N,N-dimethyl-4-aminopyridine, and a suitable solvent, such as for example dichloromethane or tetrahydrofuran, to result in an intermediate of formula (IX) (mesylate derivative) or an intermediate of formula (IX') (chloride derivative) or intermediates of formula (IX) or (IX') wherein the R^1 substituent carries a suitable protective group. Intermediates of formula (IX) or (IX') can then be reacted with an intermediate of formula (X) to obtain a compound of formula (Ia) wherein R^3 represents C_{1-6}alkyl substituted with $NR^{10}R^{11}$, said compounds being represented by formula (Ia-b) or compounds of formula (Ia-b) wherein the R^1 substituent carries a suitable protective group. This reaction may optionally be performed in the presence of a suitable base, such as for example triethylamine, K_2CO_3, Na_2CO_3 or sodium hydride and optionally a suitable solvent, such as for example acetonitrile, tetrahydrofuran, dioxane, N,N-dimethylformamide, 1-methyl-pyrrolidinone, a suitable alcohol, e.g. 1-butanol and the like. This type of reaction can also be performed with a suitable salt of the intermediate of formula (X), e.g. HCl salt of intermediate of formula (X), or may be performed in the presence of potassium iodide. In this way compounds wherein R^3 represents iodoC_{1-6}alkyl can be obtained. Compounds of formula (Ia-b) wherein the R^1 substituent carries a suitable protective group can be converted in a compound of formula (Ia-b) by reaction with a suitable acid, such as for example trifluoroacetic acid, in the presence of a suitable solvent, such as for example dichloromethane.

Intermediates of formula (IX) can also react with a suitable nitrogen containing ring within the definition of R^9, said ring being represented by formula (XXI) or a suitable salt of an intermediate of formula (XXI), in the presence of a suitable solvent, such as for example acetonitrile, 1-methyl-2-pyrrolidinone, or an alcohol, e.g. 1-butanol, optionally in the presence of potassium iodide or a suitable base, such as for example Na_2CO_3, K_2CO_3 or triethylamine, resulting in a compound of formula (Ia-d). Intermediates of formula (IX) can also react with an intermediate of formula (X-a) wherein P represents a suitable protective group, such as for example —C(═O)—O—$C(CH_3)_3$, in the presence of a suitable base, such as for example sodium hydride, and a suitable solvent, such as for example dimethylacetamide, resulting in an intermediate of formula (XXX) which can be deprotected to a compound of formula (Ia-b-1) in the presence of a suitable acid, such as for example HCl or trifluoroacetic acid, and a suitable solvent, such as for example dichloromethane or an alcohol, e.g. methanol. Intermediates of formula (XXX) can also be prepared by reacting an intermediate of formula (VI) with an intermediate of formula W_6—C_{1-6}alkyl-NR^{10}P wherein W_6 represents a suitable leaving group, such as for example halo, e.g. bromo and the like, or —O—S(═O)$_2$—CH_3, and P is as defined above, in the presence of a suitable base, such as for example sodium hydride, and a suitable solvent, e.g. N,N-dimethylformamide or N,N-dimethylacetamide. Alternatively compounds of formula (Ia-d) or (Ia-b-1) can also be prepared by reacting respectively an intermediate of formula (VI) with an intermediate of formula W_6—C_{1-6}alkyl-Ncycle or W_6—C_{1-6}alkyl-NHR^{10} wherein W_6 is as defined above.

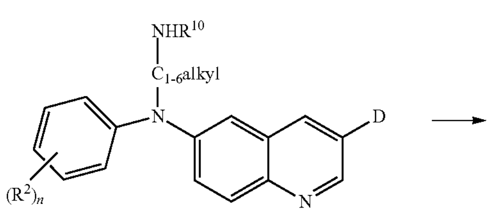
Intermediates of formula (VI) can react with W_6—R^{3d} wherein W_6 represents a suitable leaving group, such as for example halo, e.g. bromo and the like, or —O—S(=O)$_2$—CH$_3$ or p-toluenesulfonate, and R^{3d} represents optionally substituted C$_{1-6}$alkyl, such as for example —CH$_2$—C$_3$H$_5$, in the presence of a suitable base, such as for example sodium hydride or Cs_2CO_3, and a suitable solvent, such as for example N,N-dimethylformamide, N,N-dimethylacetamide or acetonitrile, resulting in a compound of formula (Ia-c). W$_6$—R^{3d} can also be used in an appropriate salt form, e.g. a hydrochloric acid salt of W$_6$—R^{3d}. In this way, compounds of formula (Ia-c) wherein R^3 represents —S(=O)$_2$—N(CH$_3$)$_2$ can also be prepared by reacting an intermediate of formula (VI) with dimethylsulfamoyl chloride, in the presence of a suitable base, such as for example NaH, and a suitable solvent, such as for example N,N-dimethylformamide. This type of reaction can also be used to prepare an intermediate wherein the R^{3d} moiety is protected by an appropriate protective group, such as for example triphenylmethyl or —CH$_2$—O—CH$_2$—CH$_2$—Si(CH$_3$)$_3$, which can then be deprotected to a compound of formula (Ia-c) in the presence of a suitable acid, such as for example HCl or trifluoroacetic acid, in a suitable solvent, such as for example dichloromethane or acetonitrile, or by reaction with a suitable desilylating agent, such as for example tetrabutylammonium fluoride in the presence of a suitable solvent, such as for example tetrahydrofuran. This type of reaction can also be performed in the presence of a suitable phase transfer agent, such as for example tetrabutylammonium bromide, a suitable base, such as for example potassium hydroxide, and a suitable solvent, such as for example 2-methyl-tetrahydrofuran and water.

Compounds of formula (Ia-c) wherein R^{3d} represents —CH$_2$—C(OH)(R')(R") wherein R' represents optionally substituted C$_{1-4}$alkyl and R" represents hydrogen or optionally substituted C$_{1-4}$alkyl, said compounds being represented by formula (Ia-c-1), can be prepared by reacting the intermediate of formula (VI) with an intermediate of formula (XXII) in the presence of a suitable base, such as for example sodium hydride, Cs_2CO_3, or potassium hydroxide, and a suitable solvent, such as for example N,N-dimethylformamide, N,N-dimethylacetamide, acetonitrile or water.

Intermediates of formula (IV) can also react with an intermediate of formula (XXIII) in the presence of a suitable catalyst, such as for example palladium (II) acetate or tris(dibenzylideneacetone)dipalladium (0), a suitable base, such as for example sodium tert-butoxide, a suitable ligand, such as for example 1, 1'-[1,1'-binaphthalene]-2,2'-diylbis[1,1-diphenylphosphine] or 2-dicyclohexylphosphino-2'-(N,N-dimethylamino)biphenyl, and a suitable solvent, such as for example dioxane, resulting in a compound of formula (Ia-c).

Compounds of formula (Ia-b) wherein R^{11} is C$_{1-6}$alkyl substituted with amino, said compounds being represented by formula (Ia-b-2), can also be prepared according to the following reaction Scheme 1A.

Scheme 1A



(Ia-b-1)

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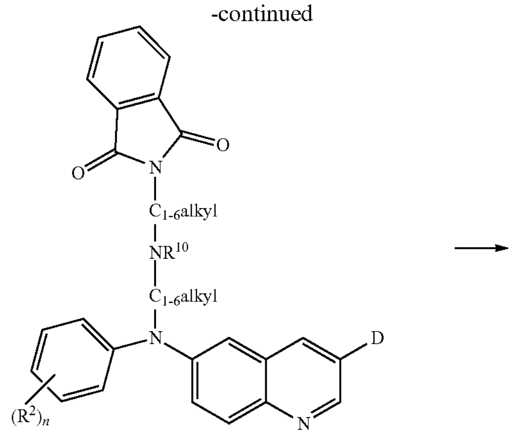
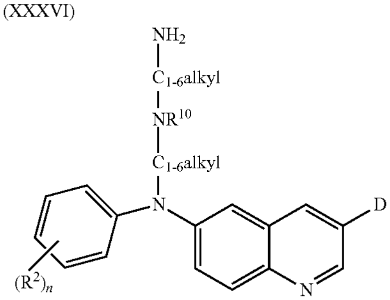


(XXXVI)

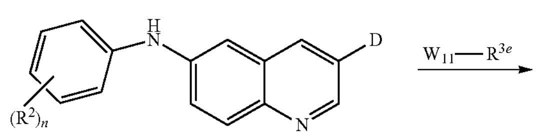


(Ia-b-2)

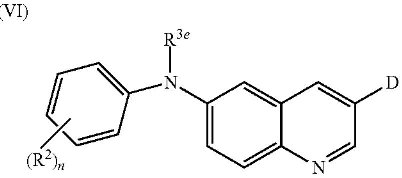
In Scheme 1A, a compound of formula (Ia-b-1) is reacted with N-(haloC$_{1-6}$alkyl)phtalimide in the presence of a suitable base, such as for example potassium carbonate, and a suitable solvent, such as for example acetonitrile, resulting in an intermediate of formula (XXXVI) which can be converted into a compound of formula (Ia-b-2) by reaction with hydrazine in the presence of a suitable solvent, such as for example an alcohol, e.g. ethanol.

Compounds of formula (Ia) wherein R^3 represents optionally substituted C$_{2-6}$alkynyl, said compounds being represented by formula (Ia-k), can be prepared according to reaction Scheme 1B.

Scheme 1B



(VI)

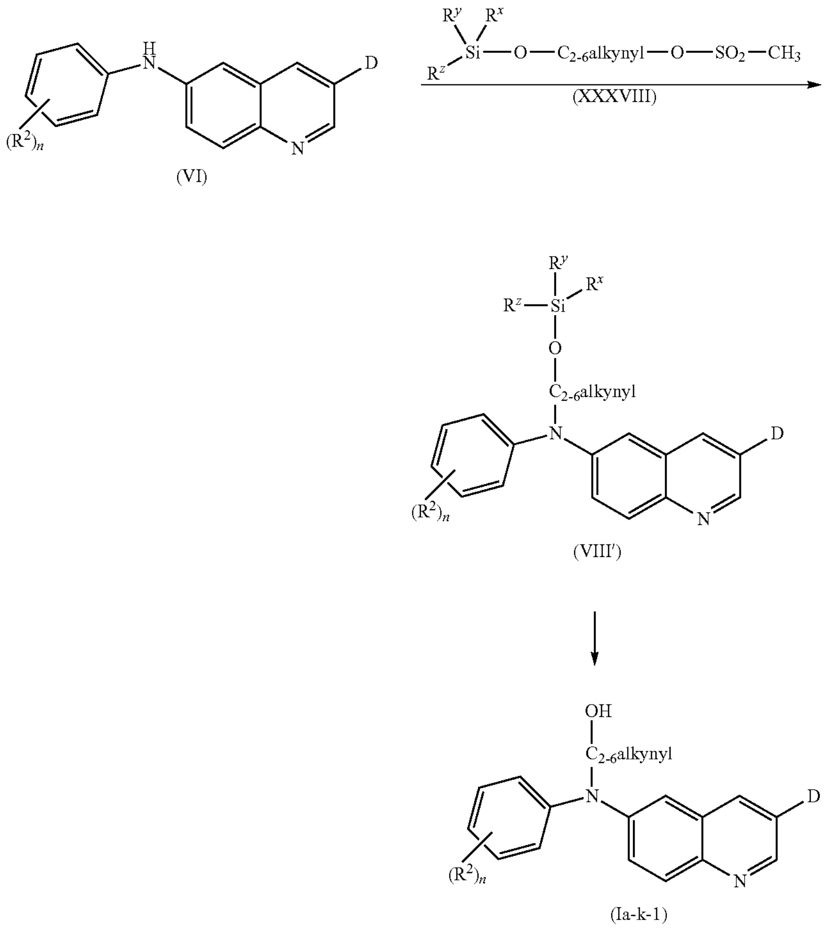


(Ia-k)

In Scheme 1B, an intermediate of formula (VI) is reacted with an intermediate of formula W$_{11}$—R^{3e} wherein R^{3e} represents optionally substituted C$_{2-6}$alkynyl and W$_{11}$ represents a suitable leaving group such as for example halo, e.g. chloro, or —O—S(=O)$_2$—CH$_3$, in the presence of a suitable base, such as for example NaH, and a suitable solvent, such as for example N,N-dimethylformamide. The intermediate W_{11}—R^{3e} wherein W_{11} represents —O—S(=O)$_2$—CH_3, can be prepared by reacting the corresponding alcohol derivative with methanesulfonyl chloride in the presence of a suitable base, such as for example triethylamine or 4-dimethylaminopyridine, and a suitable solvent, such as for example dichloromethane.

Compounds of formula (Ia-k), wherein R^{3e} represents C_{2-6}alkynyl substituted with hydroxyl, said compounds being represented by formula (Ia-k-1), can be prepared according to the following reaction Scheme 1C.

Scheme 1C

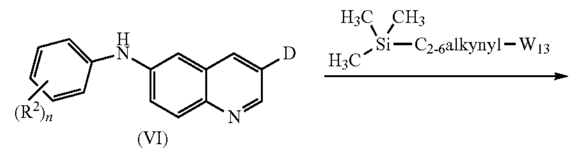


In Scheme 1C, an intermediate of formula (VI) is reacted with an intermediate of formula (XXXVIII) in the presence of a suitable base, such as for example NaH, and a suitable solvent, such as for example N,N-dimethylformamide, resulting in an intermediate of formula (VIII'), which is converted into a compound of formula (Ia-k-1) by reaction with a suitable acid, such as for example trifluoroacetic acid, in the presence of a suitable solvent, such as for example tetrahydrofuran. This reaction can also be performed with tetrabutyl ammonium fluoride in the presence of a suitable solvent such as for example tetrahydrofuran.

Alternatively, instead of an intermediate of formula (XXXVIII), halo-C_{2-6}alkynyl-O—Si(R^x)(R^y)(R^z) can also be used.

Compounds of formula (Ia-k), wherein R^{3e} represents C_{2-6}alkynyl, said compounds being represented by formula (Ia-k-2), can be prepared according to the following reaction Scheme 1D.

Scheme 1D



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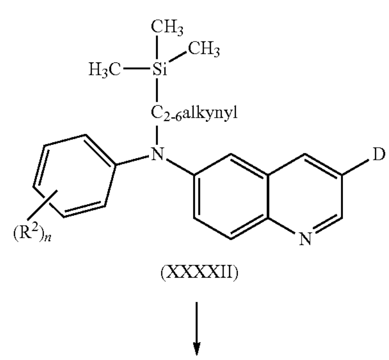

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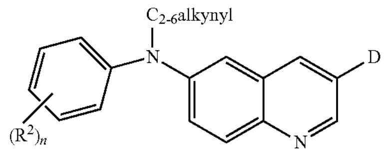
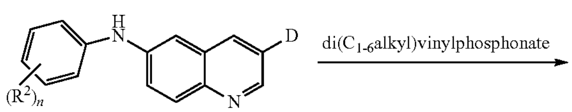


(Ia-k-2)

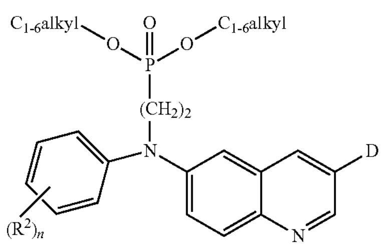
In Scheme 1D, a compound of formula (Ia-k-2) is prepared by deprotecting an intermediate of formula (XXXXII) in the presence of a suitable base, such as for example K_2CO_3, and a suitable solvent, such as for example an alcohol, e.g. methanol and the like. Said intermediate of formula (XXXXII) can be prepared by reacting an intermediate of formula (VI) with W_{13}—C_{2-6}alkynyl-$Si(CH_3)_3$ wherein W_{13} is a suitable leaving group, such as for example halogen, in the presence of a suitable base, such as for example NaH, and a suitable solvent, such as for example N,N-dimethylformamide.

Compounds of formula (Ia), wherein R^3 represents ethyl substituted with —P(═O)(OC_{1-6}alkyl$)_2$, said compounds being represented by formula (Ia-I), can be prepared according to the following reaction Scheme 1E.

Scheme 1E



(VI)

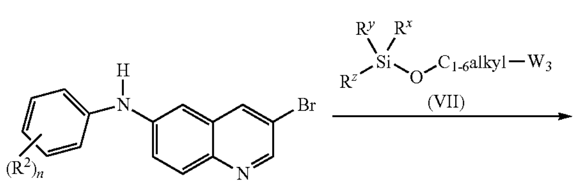


(Ia-1)

In scheme 1E, an intermediate of formula (VI) is reacted with di(C_{1-6}alkyl)vinylphosphonate in the presence of a suitable catalyst, such as for example tri-N-butylphosphine, and a suitable solvent, such as for example acetonitrile resulting in a compound of formula (Ia-I).

Intermediates of formula (VIII) can alternatively also be prepared according to the following reaction Scheme 2.

Scheme 2



(XVII)

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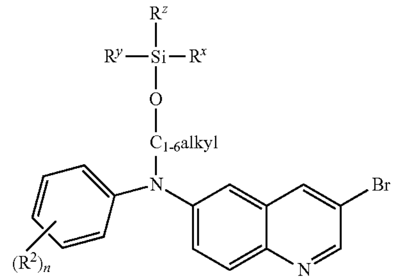
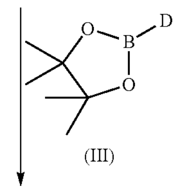
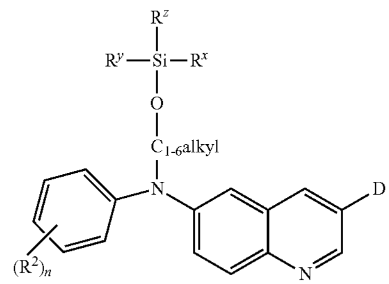


(XVIII)



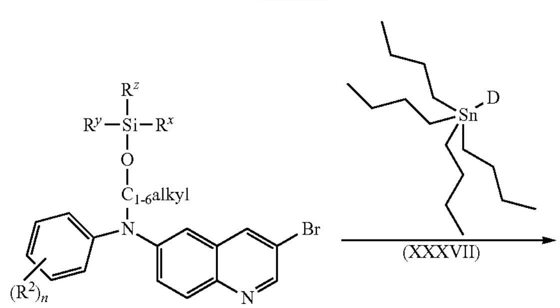


(VIII)

In Scheme 2, an intermediate of formula (XVII) is reacted with an intermediate of formula (VII) in the presence of a suitable base, such as for example sodium hydride, and a suitable solvent, such as for example N,N-dimethylformamide, resulting in an intermediate of formula (XVIII). The intermediate of formula (XVIII) can then be reacted with an intermediate of formula (III) in the presence of a suitable catalyst, such as for example $Pd_2(dba)_3$, a suitable base, such as for example K_3PO_4, a suitable ligand, such as for example 2-dicyclohexylphosphino-2',6'-dimethoxy-biphenyl, and a suitable solvent, such as for example dioxane or water or mixtures thereof.

Intermediates of formula (VIII') can be prepared according to the following reaction Scheme 3.

Scheme 3



(XVIII)

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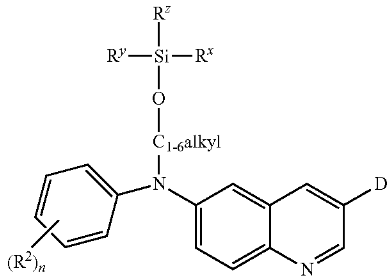
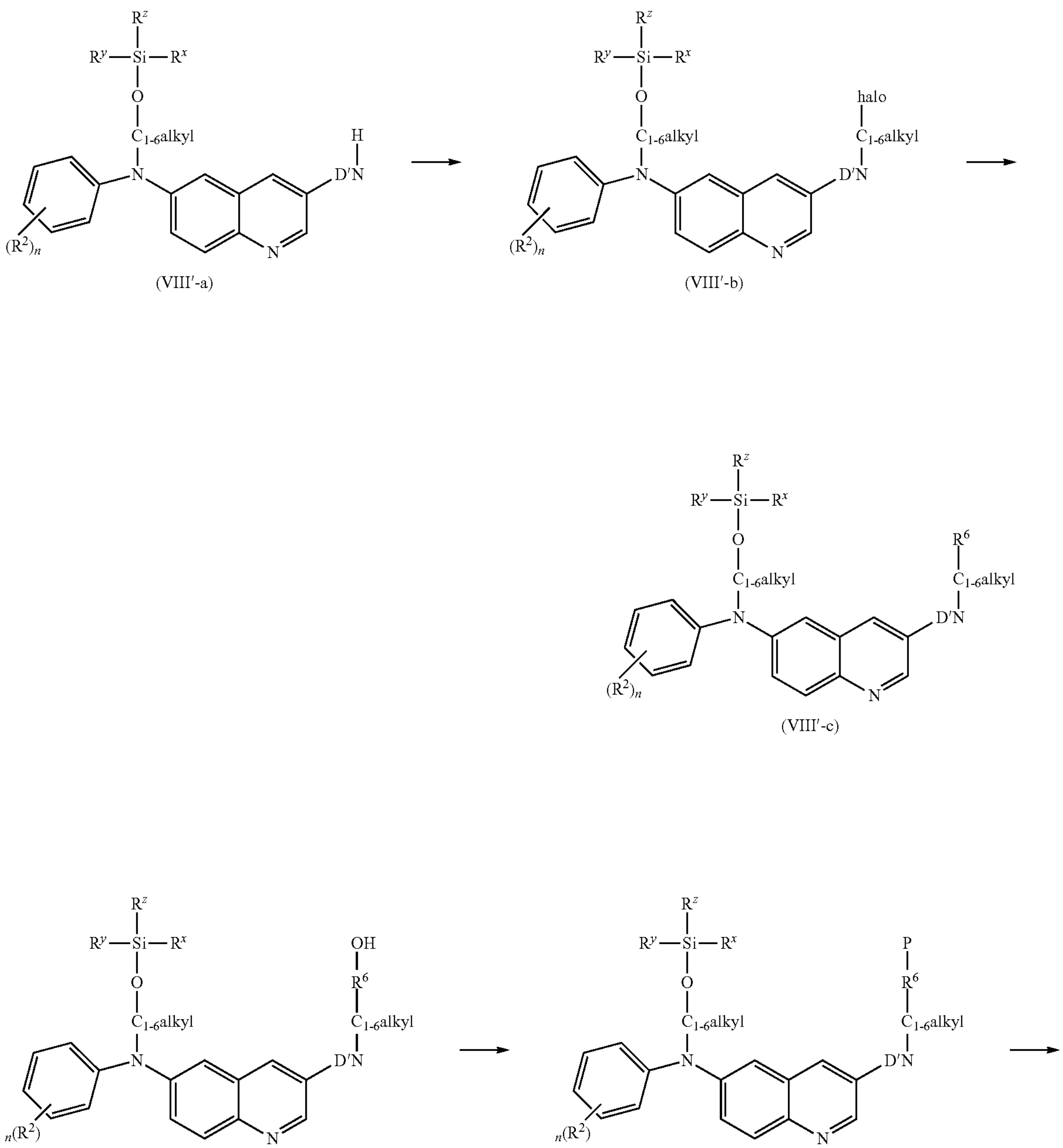


(VIII')

In Scheme 3, an intermediate of formula (XVIII) is reacted with an intermediate of formula (XXXVII) in the presence of a suitable catalyst, such as for example tetrakis (triphenylphisphine)palladium (0), and a suitable solvent, such as for example toluene.

Intermediates of formula (VIII') wherein D is a ring moiety containing a nitrogen atom, as represented in Scheme 4, can be further reacted according to the following reaction Scheme 4.

Scheme 4



(VIII'-a)

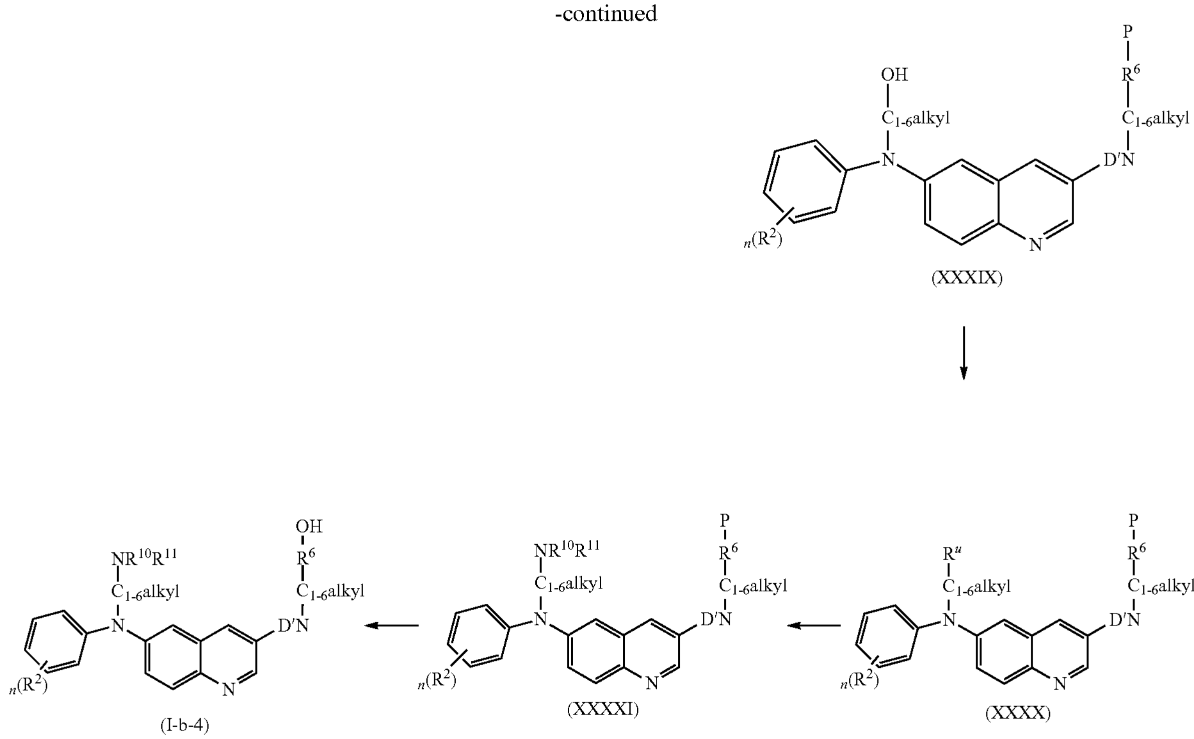
(VIII'-b)

(VIII'-c)

(VIII'-c-1)

(VIII'-c-2)

-continued



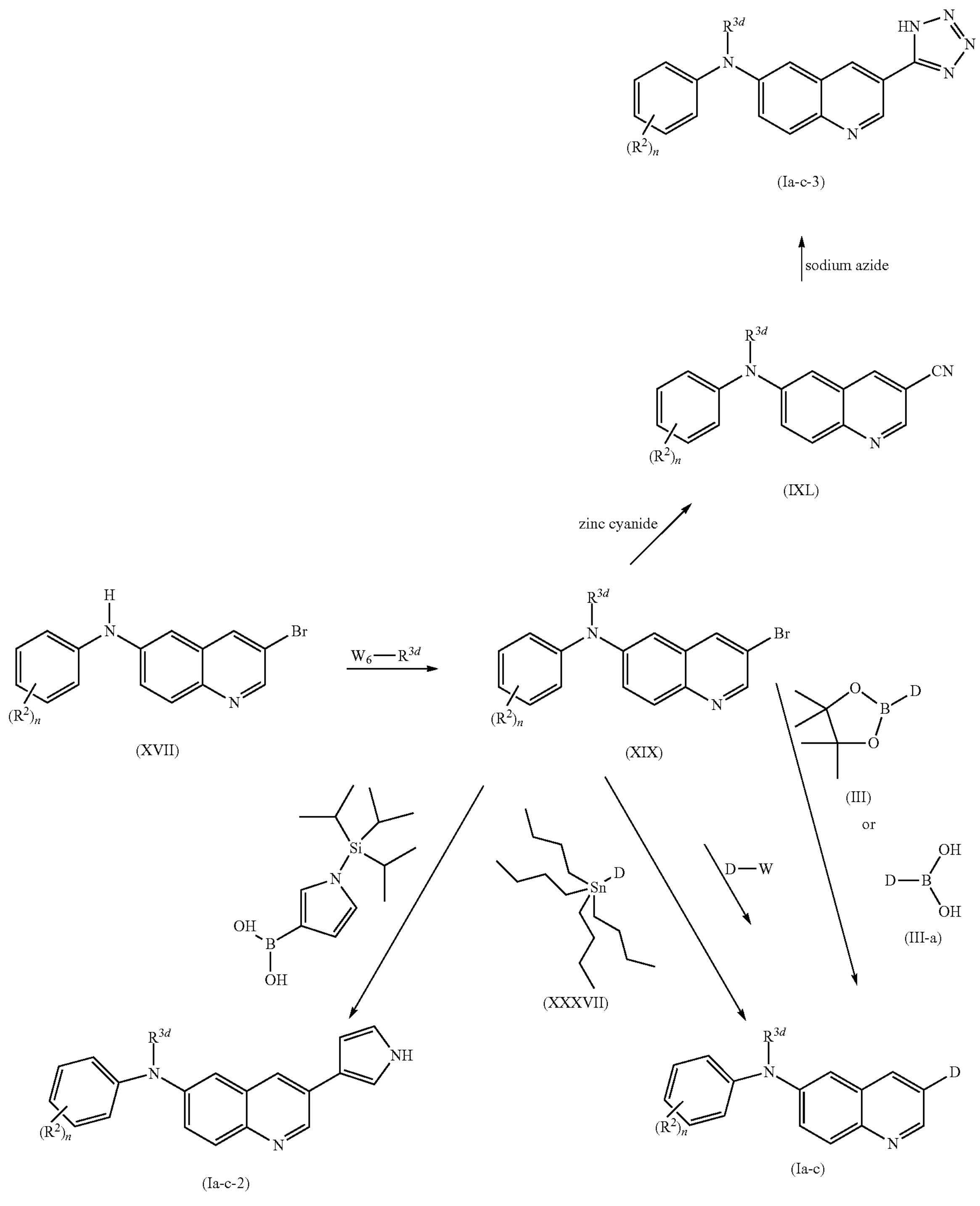
In Scheme 4, the D'N moiety represents a -D moiety wherein the D ring moiety contains a nitrogen atom. Intermediates of formula (VIII') wherein D represents D'NH, said intermediates being represented by formula (VIII'-a), can be converted into an intermediate of formula (VIII'-b) by reaction with W_{12}—C_{1-6}alkyl wherein W_{12} represents a suitable leaving group, such as for example halo, e.g. chloro, in the presence of a suitable base, such as for example NaH, and a suitable solvent, such as for example N,N-dimethylformamide. Said intermediates of formula (VIII'-b) can be converted into an intermediate of formula (VIII'-c) by reaction with R^6 in the presence of a suitable base, such as for example K_2CO_3, and a suitable solvent, such as for example acetonitrile. When in an intermediate of formula (VIII'-c) the R^6 carries a hydroxyl group as in an intermediate of formula (VIII'-c-1), then said hydroxyl group can be protected by a suitable protective group P, such as for example —O—C(═O)—C_{1-6}alkyl, by reaction with C_{1-6}alkyl-C(═O)—W_{12}, in the presence of a suitable base, such as for example triethylamine, 4-dimethylaminopyridine, and a suitable solvent, such as for example dichloromethane, resulting in an intermediate of formula (VIII'-c-2) which can be converted into an intermediate of formula (XXXIX) by reaction with tetrabutylammonium fluoride in the presence of a suitable solvent, such as for example tetrahydrofuran. Said intermediate of formula (XXXIX) can be converted into an intermediate of formula (XXXX) wherein R^u represents —SO_2CH_3, by reaction with methane sulfonyl chloride in the presence of a suitable base, such as for example triethylamine, and a suitable solvent, such as for example dichloromethane, which can be converted into an intermediate of formula (XXXXI) by reaction with an intermediate of formula (X) in a suitable solvent, such as for example acetonitrile. Said intermediate of formula (XXXXI) can then be deprotected into a compound of formula (Ia-b-4) in the presence of a suitable base, such as for example K_2CO_3, and a suitable solvent, such as for example an alcohol, e.g. methanol and the like. It is considered to be within the knowledge of the person skilled in the art to recognize for which other D ring moieties the described reactions also apply.

Intermediates of formula (VIII') can also be reacted to prepare compounds of the present invention according to the reaction schemes as presented in Scheme 1. It is considered to be within the knowledge of the skilled person to recognize in which condition and for which definitions of R^1 on the D ring moiety a protective group may be appropriate for the reactions to be carried out. For instance, a hydroxyl group within the definition of R^1 may be protected with a tert. butyldimethylsilyl moiety; a NH group within the definition of R^1 may be protected with a —C(═O)—O—C(CH_3)$_3$ group.

It is also considered to be within the knowledge of the skilled person to recognize appropriate deprotection reactions.

Compounds of formula (Ia) wherein R^3 represents optionally substituted C_{1-6}alkyl, said compounds being represented by formula (Ia-c), can also be prepared according to the below reaction Scheme 5.

Scheme 5

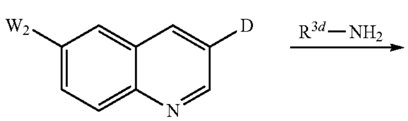


In Scheme 5, an intermediate of formula (XVII) is reacted with W_6—R^{3d} wherein W_6 represents a suitable leaving group, such as for example halo, e.g. bromo and the like, and R^{3d} represents optionally substituted C_{1-6}alkyl, such as for example CH_2—C_3H_5, in the presence of a suitable base, such as for example sodium hydride, and a suitable solvent, such as for example N,N-dimethylformamide, resulting in an intermediate of formula (XIX). In a next step, the intermediate of formula (XIX) is reacted with an intermediate of formula (III) or (III-a) in the presence of a suitable catalyst, such as for example tetrakis(triphenyl)phosphine palladium or $Pd_2(dba)_3$ (tris(dibenzylideneacetone) dipalladium (0)), optionally a suitable ligand, such as 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl, a suitable base, such as for example Na_2CO_3 or K_3PO_4, and a suitable solvent, such as for example ethylene glycol dimethylether or dioxane or water. Or the intermediate of formula (XIX) is reacted with an intermediate of formula (XXXVII) in the presence of a suitable catalyst, such as for example tetrakis (triphenyl)phosphine palladium, and a suitable solvent, such as for example N,N-dimethylformamide or toluene. Or the intermediate of formula (XIX) is reacted with D-W, wherein W represents a suitable leaving group, such as for example halo, e.g. bromo, iodod and the like, in the presence of a suitable catalyst, such as for example tetrakis(triphenyl) phosphine palladium, ethylmagnesium chloride, zinc chloride to generate in situ a reactive organometallic species, and a suitable solvent, such as for example tetrahydrofuran. An intermediate of formula (XIX) can also react with a suitable ring moiety represented by D, e.g. imidazole or 4-methylimidazole or 3-methylpyrazole or 2-methylimidazole, in the presence of a suitable catalyst, such as for example tris (dibenzylideneacetone) dipalladium (0), a suitable ligand, such as for example Rac-bis(diphenylphosphino)-1,1'-binaphthyl, in the presence of a suitable base, such as for example sodium tert-butoxide, and a suitable solvent, such as for example toluene to obtain the corresponding final compound.

An intermediate of formula (XIX) can also react with 1-(triisopropylsilyl)pyrrole-3-boronic acid, in the presence of a suitable catalyst, such as for example tetrakis(triphenyl) phosphine palladium, a suitable base, such as for example sodium carbonate, or a suitable deprotective reagent, such as for example tetrabutylammonium fluoride, to cleave C-Silicon bond, and a suitable solvent, such as for example ethylene glycol dimethylether, to obtain a compound of formula (Ia-c-2). An intermediate of formula (XIX) can react with zinc cyanide in the presence of a suitable catalyst, such as for example tetrakis(triphenyl)phosphine palladium, a suitable ligand, such as for example triphenylphosphine, and a suitable solvent, such as for example acetonitrile. The resulting intermediate of formula (IXL) can react with sodium azide and ammonium chloride in the presence of a suitable solvent, such as for example N,N-dimethylformamide, to obtain a compound of formula (Ia-c-3). It is considered to be within the knowledge of the skilled person to recognize that instead of R^{3d}, also a suitable protected form of R^{3d} can be used.

Compounds of formula (Ia-c) can alternatively also be prepared according to the below reaction Scheme 6.

Scheme 6



(IV)

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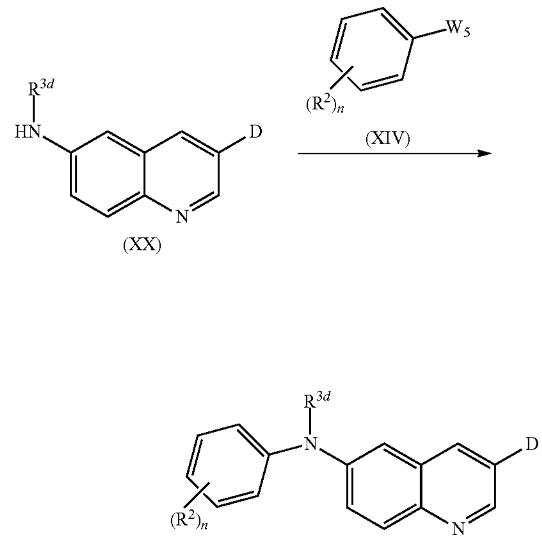


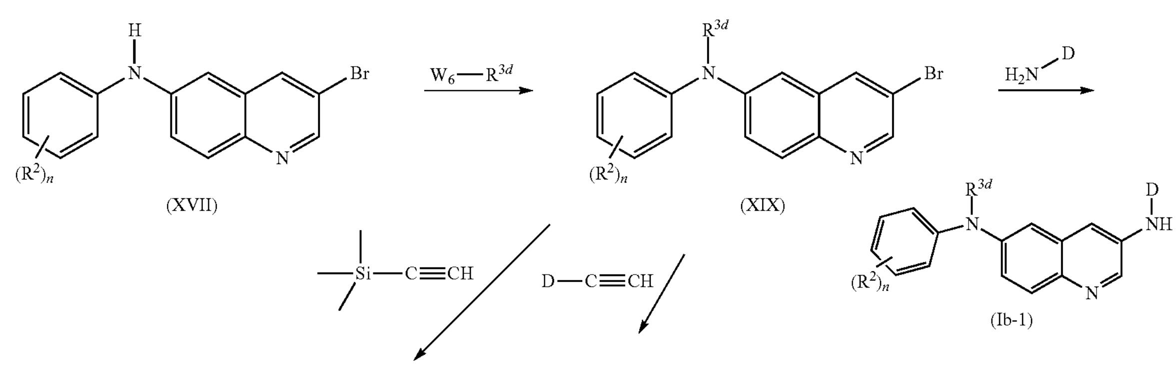
(XX)

(Ia-c)

In Scheme 6, an intermediate of formula (IV) is reacted with R^{3d}—NH_2 in the presence of a suitable catalyst, such as for example palladium (II) acetate, a suitable base, such as for example sodium tert-butoxide, and a suitable ligand, such as for example 1,1-[1 μl'-binaphthalene]-2,2'-diylbis[1, 1-diphenylphosphine], resulting in an intermediate of formula (XX) which is reacted in a next step with an intermediate of formula (XIV) in the presence of a suitable catalyst, such as for example palladium (II) acetate or $Pd_2(dba)_3$ (tris(dibenzylidene acetone) dipalladium (0)), a suitable ligand such as for example 2-dicyclohexylphosphino-tris-isopropyl-biphenyl or 1,1'-[1,1'-binaphthalene]-2,2'-diylbis [1,1-diphenylphosphine], a suitable base, such as for example sodium tert-butoxide, and a suitable solvent, such as for example ethylene glycol dimethylether.

Compounds of formula (I) wherein R^3 represents optionally substituted C_{1-6}alkyl, and wherein Y is E-D and E is other than a bond, said compounds being represented by formula (Ib) can be prepared according to the below reaction Scheme 7.

Scheme 7



(XVII)

(XIX)

(Ib-1)

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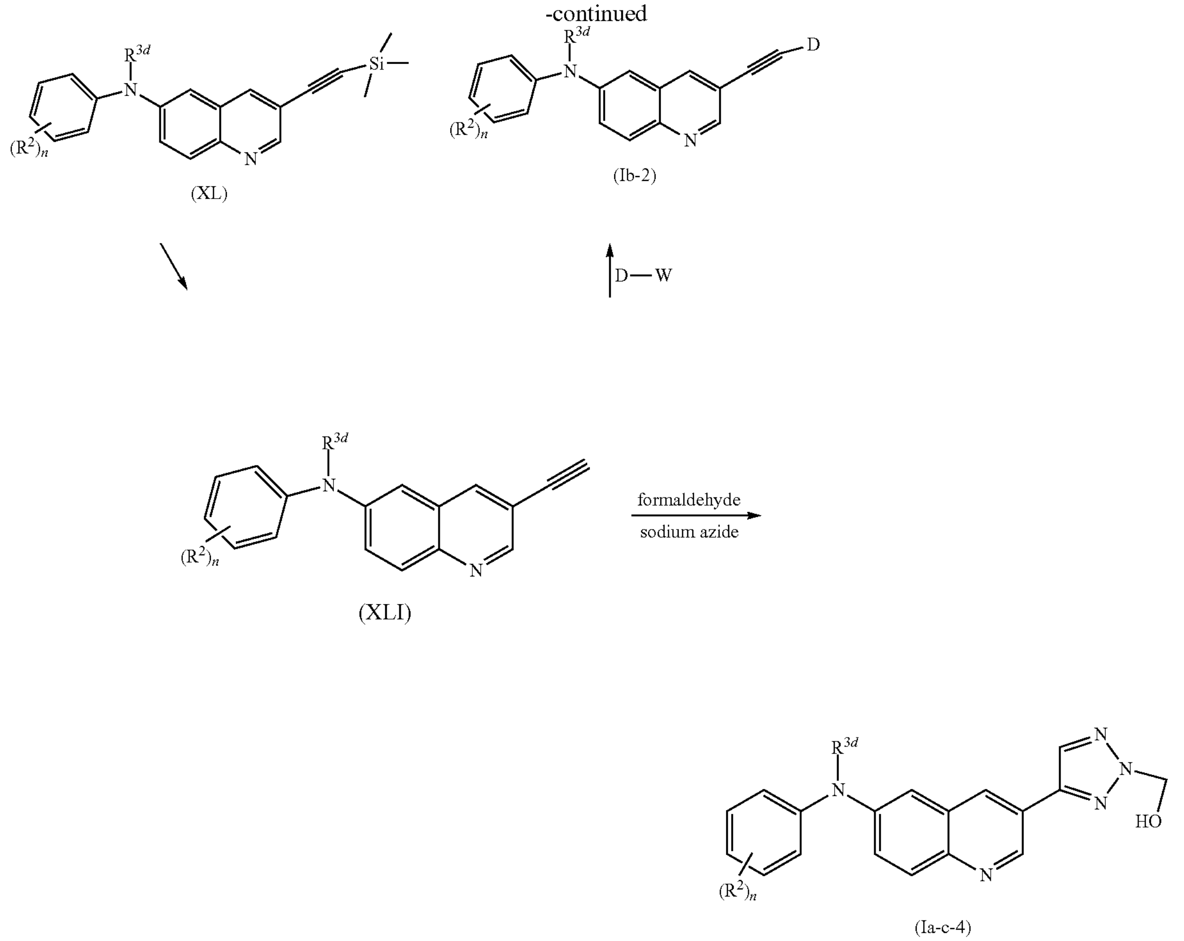


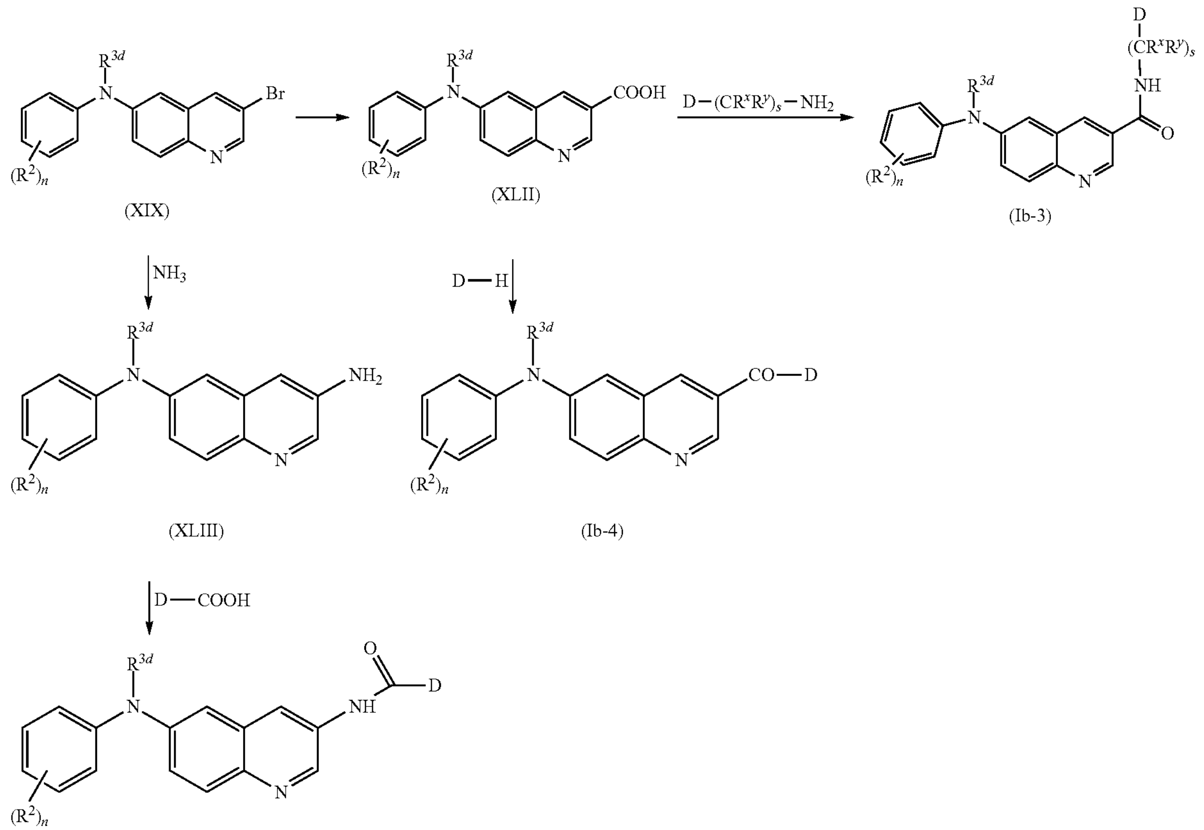
In Scheme 7, an intermediate of formula (XIX) is reacted with D-NH_2 in the presence of a suitable catalyst, such as for example palladium (II) acetate, a suitable base, such as for example sodium tert-butoxide, and a suitable ligand, such as for example 1,1'-[1,1'-binaphthalene]-2,2'-diylbis[1,1-diphenylphosphine], resulting in a compound of formula (Ib-1). Or an intermediate of formula (XIX) is reacted with

$$D{-}{\equiv}{-}CH,$$

in the presence of a suitable catalyst, such as for example dichlorobis(triphenylphosphine) palladium (II) and copperiodide, a suitable ligand, such as for example triphenylphosphine, a suitable base, such as for example triethylamine, and a suitable solvent, such as for example N,N-dimethylformamide to obtain a compound of formula (Ib-2). A compound of formula (Ib-2) can also be prepared by reacting an intermediate of formula (XLI) with D-W as defined above, in the presence of a suitable catalyst, such as for example dichlorobis(triphenylphosphine) palladium (II) and copperiodide, a suitable base, such as for example triethylamine, and a suitable solvent, such as for example N,N-dimethylformamide and acetonitrile. The intermediate of formula (XLI) can be prepared by reacting an intermediate of (XIX) with (trimethylsilyl)acetylene in the presence of a suitable catalyst, such as for example dichlorobis (triphenylphosphine) palladium (II) and copperiodide, a suitable ligand, such as for example triphenylphosphine, a suitable base, such as for example triethylamine, and a suitable solvent, such as for example dimethylsulfoxide, followed by reacting the resulting intermediate of formula (XL) with potassium carbonate in a suitable solvent, such as for example an alcohol, e.g. methanol. The intermediate of formula (XLI) can also react with 2-(4-morpholino)ethylazide, in the presence of a suitable catalyst, such as for example copper iodide, a suitable base, such as for example N,N-diisopropylethylamine, and a suitable solvent, such as for example tetrahydrofuran, to obtain a compound wherein E is a bond and D is 2-(4-morpholino)ethyl-1-triazolyl. An intermediate of formula (XLI) can also react with sodium azide and formaldehyde in the presence of a suitable catalyst, such as for example copper sulfate and sodium L ascorbate, and a suitable solvent, such as for example dioxane and acetic acid, to obtain a compound of formula (IA-c-4).

Compounds of formula (Ib) can also be prepared according to the below reaction Scheme 7B.

Scheme 7B

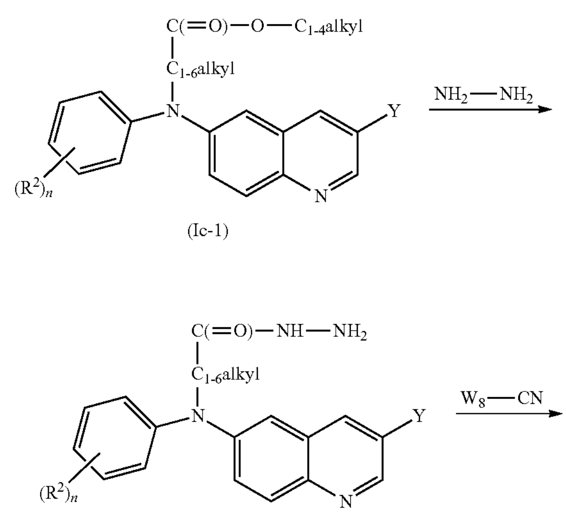


(XIX) (XLII) (Ib-3) (XLIII) (Ib-4) (Ib-5)

In Scheme 7B, an intermediate of formula (XIX) is reacted with CO gaz, potassium acetate, in the presence of a suitable catalyst, such as for example tetrakis(triphenyl) phosphine palladium, and a suitable solvent, such as for example dioxane. The resulting intermediate of formula (XLII) is reacted with D-$(CR^xR^y)_s$—NH_2 in the presence of suitable peptide coupling reagents such as for example 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and 1-hydroxybenzotriazole, a suitable base, such as for example triethylamine, and a suitable solvent, such as for example methylene chloride, to obtain a compound of formula (Ib-3). The intermediate of formula (XLII) can also react with D-H in the presence of suitable peptide coupling reagents such as for example 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and 1-hydroxybenzotriazole, a suitable base, such as for example triethylamine, and a suitable solvent, such as for example methylene chloride to obtain a compound of formula (Ib-4). An intermediate of formula (XIX) can also react with NH_3 in the presence of a suitable catalyst such as for example $Pd[P(o\text{-}tol)_3]_2$, a suitable ligand such as for example CyPF-t-Bu (Josiphos ligand), a suitable base such as for example sodium tert-butoxide, a suitable sovent such as for example 1,4-dioxane, to obtain intermediate (XLIII), which can react with D-COOH, in the presence of suitable peptide coupling reagents such as for example 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and 1-hydroxybenzotriazole, a suitable base, such as for example triethylamine, and a suitable solvent, such as for example methylene chloride to obtain a compound of formula (Ib-5).

Compounds of formula (I) wherein W is —NR^3—, said compound being represented by formula (Ic), and said R^3 is C_{1-6}alkyl substituted with 5-amino-1,3,4-oxadiazolyl can be prepared according to the below reaction Scheme 8.

Scheme 8



(Ic-1) (XXXI)

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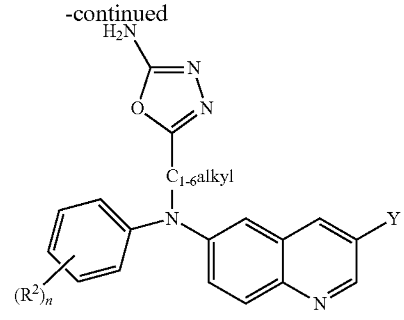
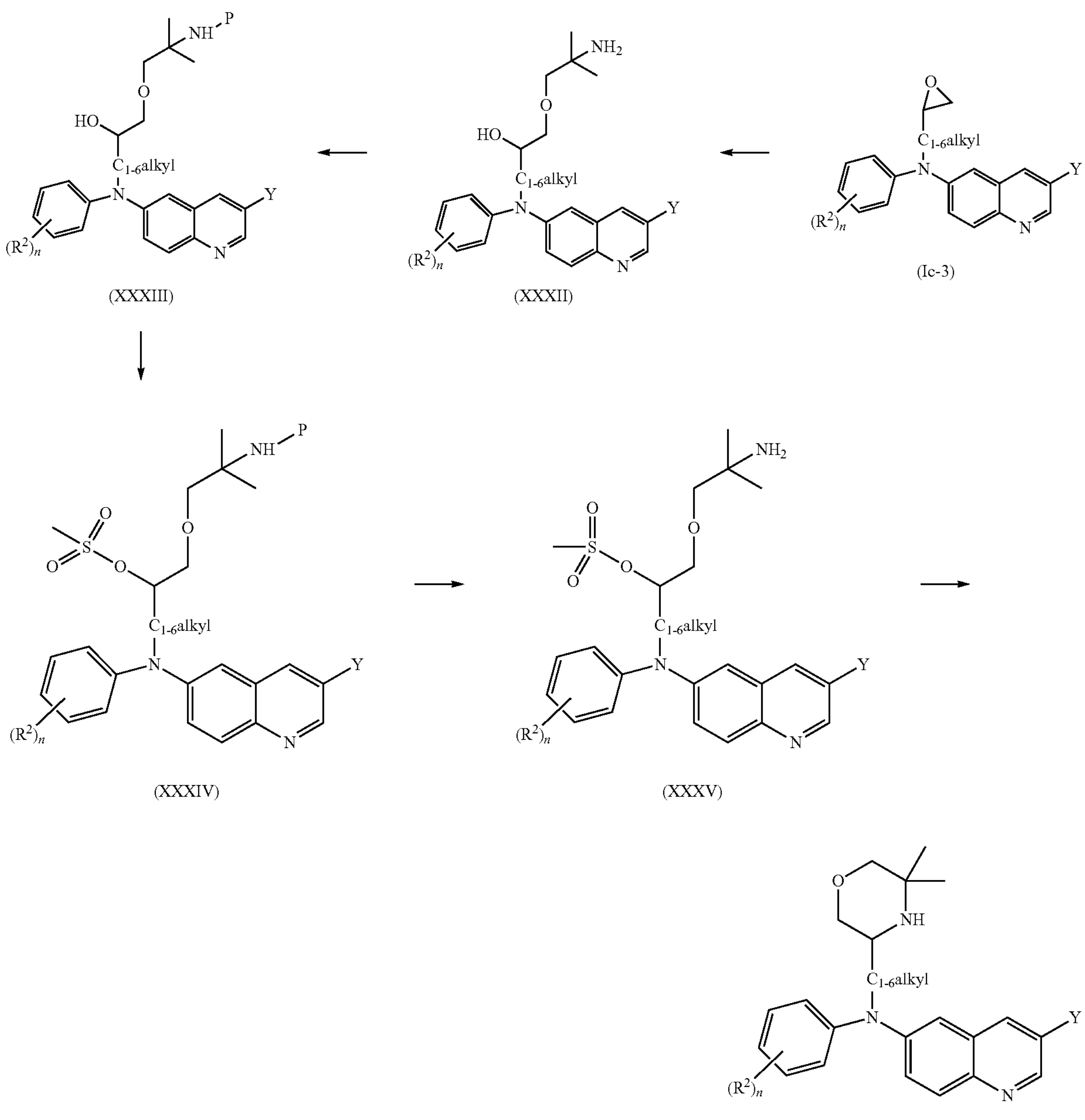


(Ic-2)

In Scheme 8, a compound of formula (Ic-1) is reacted with NH_2—NH_2 in the presence of a suitable solvent, such as for example an alcohol, e.g. ethanol resulting in an intermediate of formula (XXXI) which is then reacted in a next step with W_8—CN, wherein W_8 represents a suitable leaving group, such as for example halo, e.g. bromo, in the presence of a suitable base, such as for example $NaHCO_3$, and a suitable solvent, such as for example water or dioxane.

Compounds of formula (Ic) wherein R^3 is C_{1-6}alkyl substituted with 3,3-dimethyl-morpholine can be prepared according to the below reaction Scheme 8A.

Scheme 8A

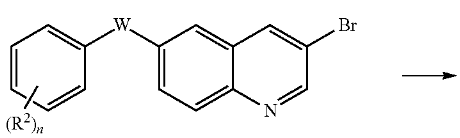


(Ic-4)

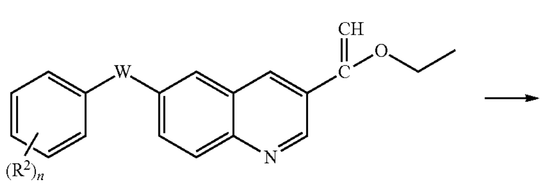
In Scheme 8A, a compound of formula (Ic-3) is reacted with 2-amino-2-methyl-1-propanol in the presence of a suitable base, such as for example NaH and in the presence of a suitable solvent, such as for example N,N-dimethylformamide resulting in an intermediate of formula (XXXII) of which the NH_2 moiety is protected by a suitable protecting group P, such as for example C(=O)—O—C(CH_3)$_3$, by reaction with for instance di-tert-butyl dicarbonate in the presence of a suitable solvent, such as for example dioxane, and a suitable base, such as for example $NaHCO_3$, resulting in an intermediate of formula (XXXIII). In a next step, said intermediate is reacted with methanesulfonyl chloride in the presence of a suitable solvent, such as for example dichloromethane, and a suitable base, such as for example triethylamine resulting in an intermediate of formula (XXXIV) which is converted into an intermediate of formula (XXXV) by reaction with a suitable acid, such as for example trifluoroacetic acid, in the presence of a suitable solvent, such as for example dichloromethane. The intermediate of formula (XXXV) is converted into a compound of formula (Ic-4) by reaction with a suitable base, such as for example N,N-diisopropylethylamine and triethylamine in the presence of a suitable solvent, such as for example an alcohol, e.g. methanol.

In general, compounds of formula (I) wherein Y represents —CR^{18}═N—OR^{19}, said compounds being represented by formula (Id), can be prepared as in Scheme 9.

Scheme 9

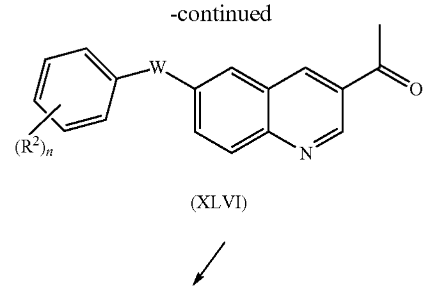


(XLIV)

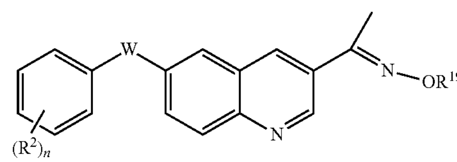


(XLV)

-continued



(XLVI)



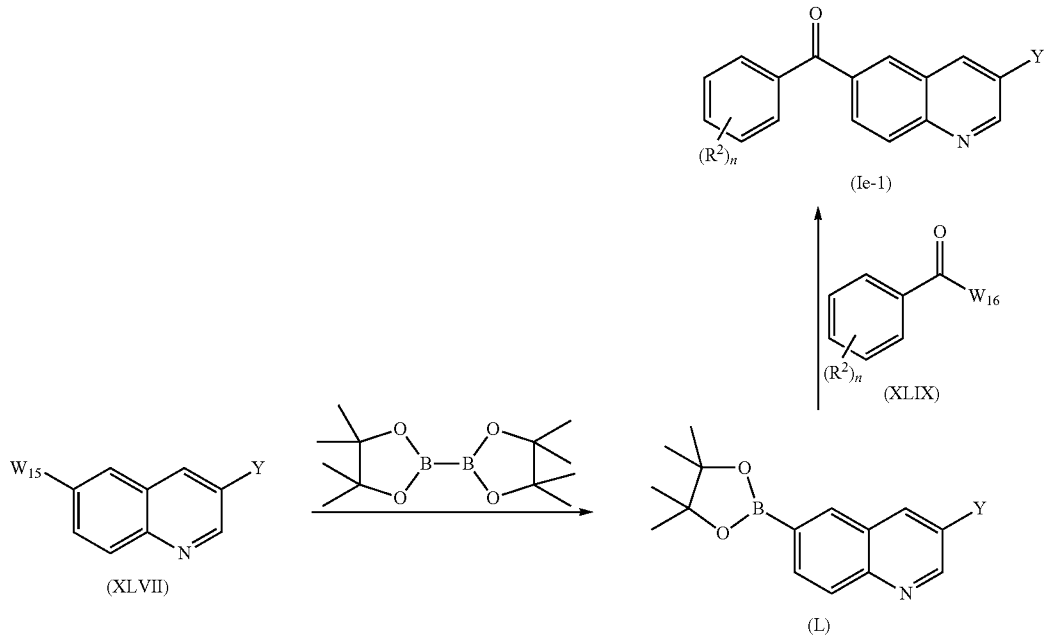
(Id-1)

In Scheme 9, an intermediate of formula (XLIV) is reacted with tributyl(1-ethoxyvinyl)tin, in the presence of a suitable catalyst, such as for example dichlorobis(triphenylphosphine) palladium (II) and optionally in the presence of copperiodide and a suitable ligand, such as for example triphenylphosphine, and in the presence of a suitable solvent, such as for example N,N-dimethylformamide, followed by reacting the resulting intermediate of formula (XLV) with a suitable acid, such as for example hydrochloric acid, and a suitable solvent, such as for example acetone. The obtained intermediate of formula (XLVI) is then reacted with R^{19}—O—NH_2 in the presence of a suitable base such as for example pyridine, and a suitable solvent, such as for example an alcohol, e.g. ethanol, resulting in a compound of formula (Id-1). A preferred intermediate of formula (XLIV) is the intermediate of formula (XIX).

An intermediate of formula (XLVI) can also be converted into a compound of formula (I) wherein E is a direct bond and D is 3-methyl-oxazole or oxazole, by reaction with 1-methyl-1-tosylmethyl isocyanide or tosylmethyl isocyanide, in the presence of a suitable base, such as for example dipotassium carbonate, and a suitable solvent, such as for example an alcohol, e.g. methanol.

In general, compounds of formula (I) wherein W is —C($R^{3a}R^{3b}$)—, said compounds being represented by formula (Ie) can be prepared according to the following reaction Scheme 10.

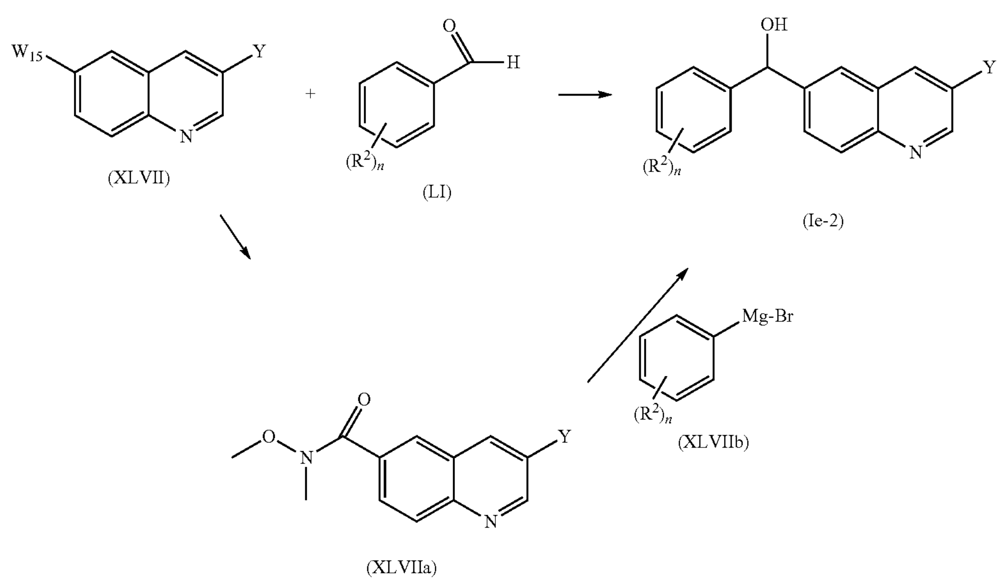
Scheme 10



In scheme 10, a compound of formula (Ie-1) is prepared by reacting an intermediate of formula (XLVII) wherein W_{15} represents a suitable group, such as for example halo, e.g. bromo and the like, with bis(pinacolato)diboron in the presence of a suitable catalyst, such as for example $PdCl_2$, and a suitable ligand, such as for example 1,1-bis(diphenylphosphino)ferrocene, in the presence of a base, such as for example potassium acetate, and a suitable solvent, such as for example dioxane, followed by reacting the resulting intermediate of formula (L) with an intermediate of formula (XLIX) wherein W_{16} represents a suitable leaving group, such as for example halo, e.g. chloro and the like, in the presence of a catalyst, such as for example dichlorobis(triphenylphosphine)palladium, a suitable base, such as for example Na_2CO_3, and a suitable solvent, such as for example tetrahydrofuran.

Compounds of formula (Ie) can also be prepared according to the following reaction Scheme 11.

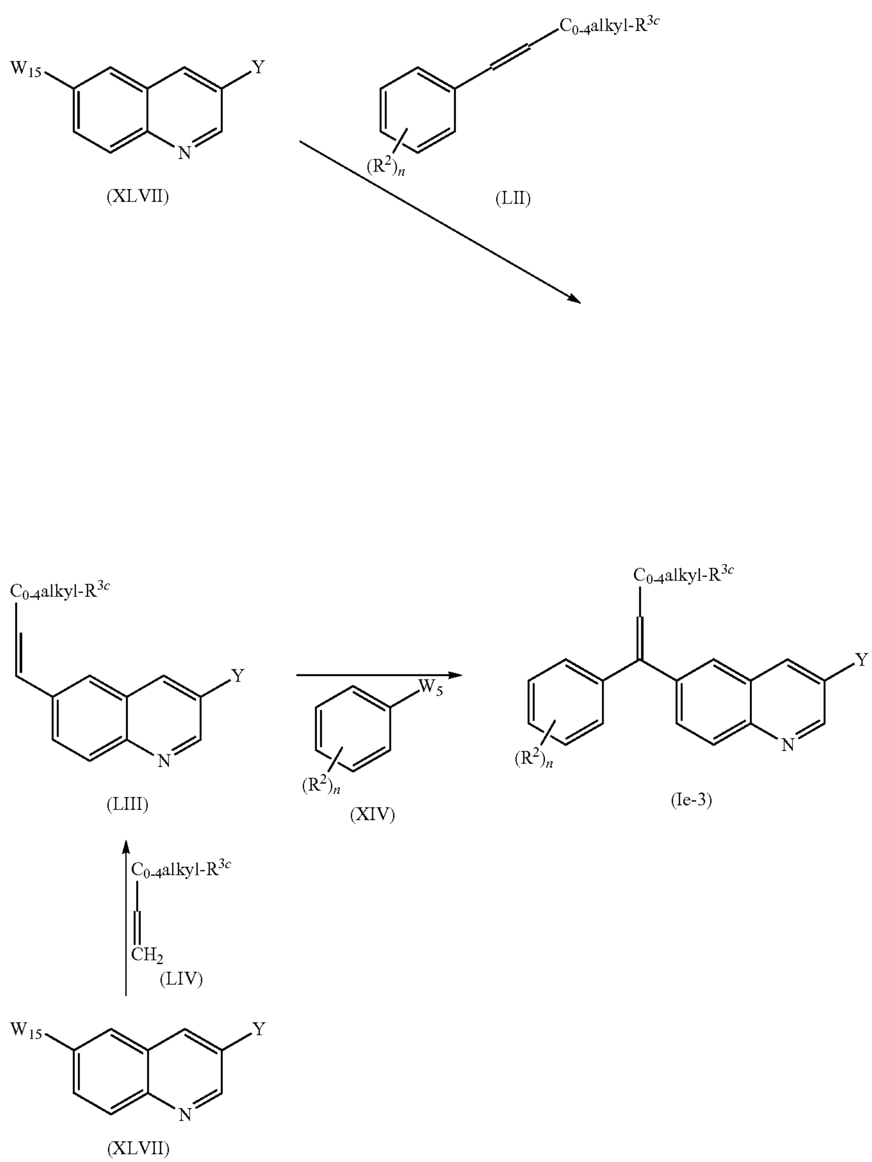
Scheme 11



In Scheme 11, an intermediate of formula (XLVII) is reacted with an intermediate of formula (LI) in the presence of isopropylmagnesium chloride to prepare the magnesium chloride derivative of XLVII and a suitable solvent, such as for example tetrahydrofuran. An intermediate of formula (XLVII) can also react with N,O-dimethylhydroxylamine hydrochloride in the presence of a suitable catalyst, such as for example $Pd(Ph_3)_4$, a suitable base, such as for example triethylamine, and a suitable solvent, such as for example toluene, to result in an intermediate of formula (XLVIIa) which can react with an intermediate of formula (XLVIIb) in the presence of a suitable solvent, such as for example tetrahydrofuran, to result in a compound of formula (Ie-2).

Compounds of formula (Ie) can also be prepared according to the following reaction Scheme 12.

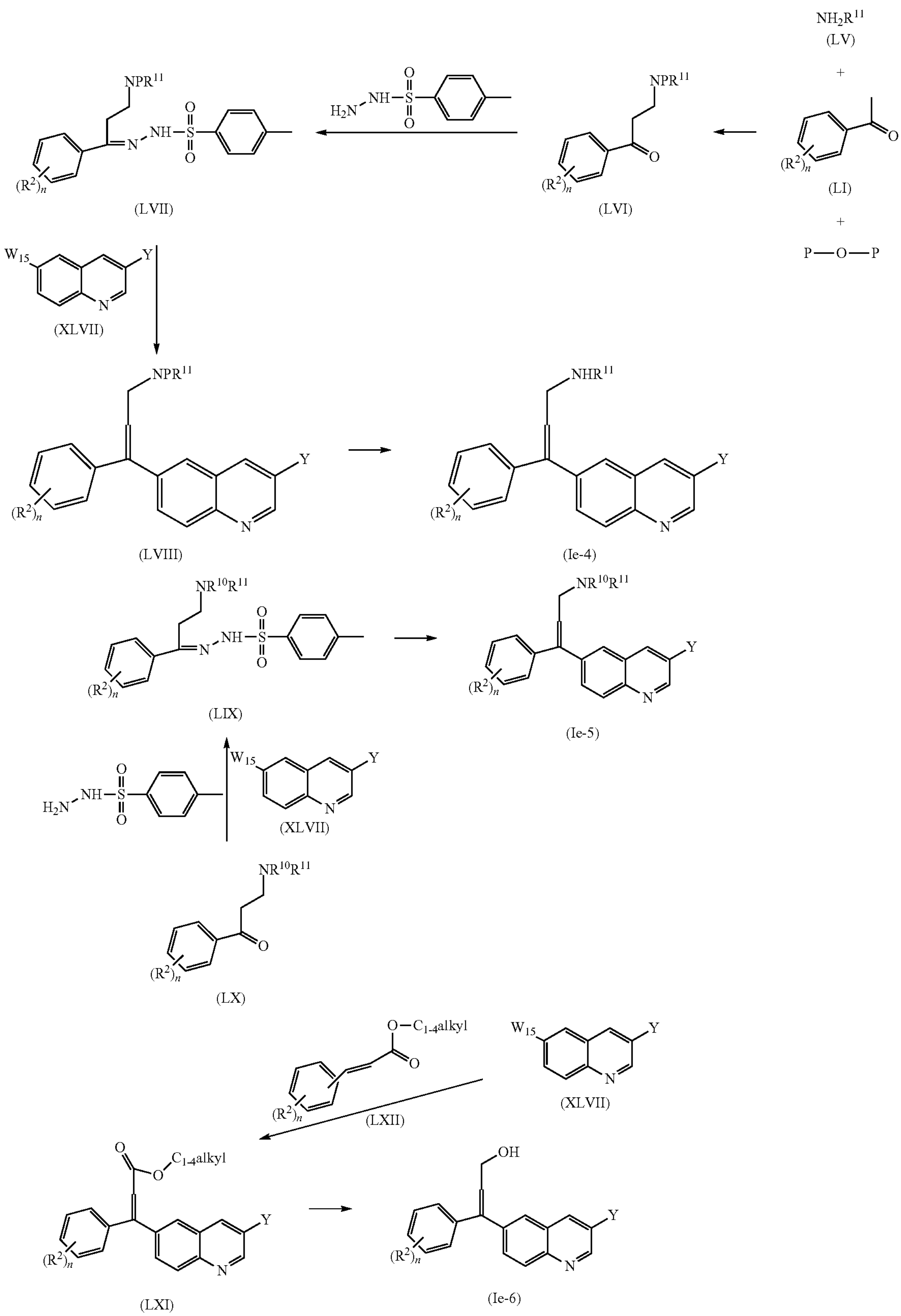
Scheme 12



In Scheme 12, intermediates of formula (XLVII) are reacted with an intermediate of formula (LII) in the presence of a suitable catalyst, such as for example palladium(II) acetate, a suitable base, such as for example potassium acetate, and tetrabutylammonium bromide as a phase transfer agent, and a suitable solvent, such as for example N,N-dimethylformamide, to give a compound of formula (Ie-3). Compounds of formula (Ie-3) can also be prepared by reacting an intermediate of formula (XLVII) with an intermediate of formula (LIV) in the presence of a suitable catalyst, such as for example palladium(II)acetate, a suitable ligand, such as for example tri-o-tolylphosphine, a suitable base, such as for example triethylamine, and a suitable solvent, such as for example acetonitrile, resulting in an intermediate of formula (LIII), which can then be reacted with an intermediate of formula (XIV) wherein W_5 represents a suitable leaving group, such as for example halo, e.g. bromo, in the presence of a suitable catalyst, such as for example palladium(II)acetate, a suitable base, such as for example potassium acetate, and tetrabutylammonium bromide as solid base, and a suitable solvent, such as for example N,N-dimethylformamide.

Compounds of formula (Ie) can also be prepared according to the following reaction Scheme 13.

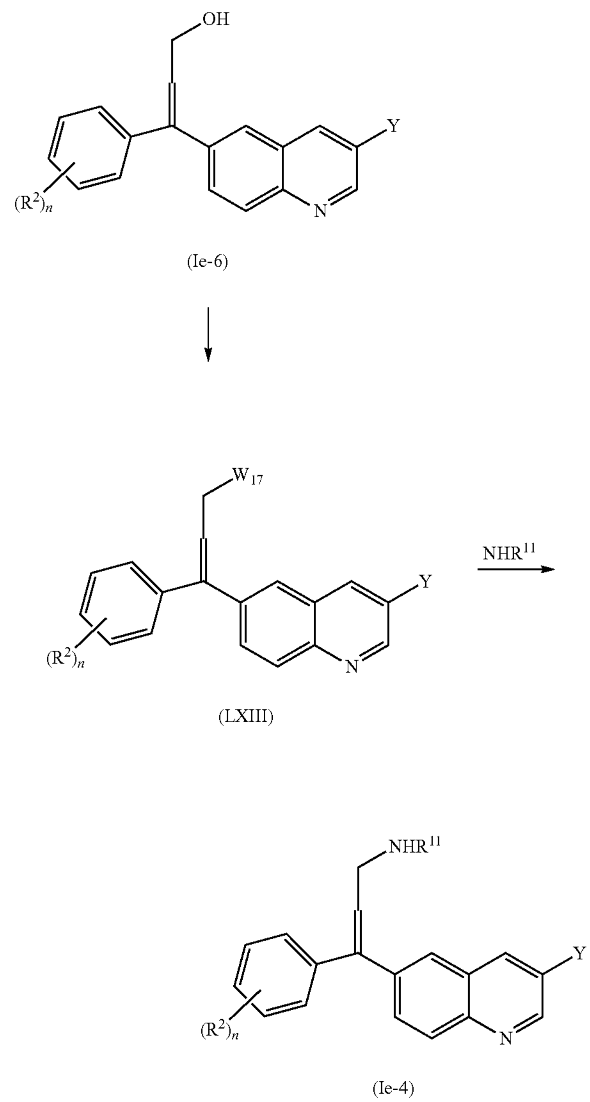
Scheme 13


NH2R11
(LV)
+
(LI)
+
P—O—P
NPR11
(LVI)
H2N NH S O O
NPR11
NH S O O N
(R2)n
(LVII)
W15
Y
N
(XLVII)
NPR11
(LVIII)
NHR11
(Ie-4)
NR10R11
(LIX)
(Ie-5)
(LX)
O—C1-4alkyl
(LXII)
C1-4alkyl
(LXI)
OH
(Ie-6)

In Scheme 13, an intermediate of formula (LV) preferably in its salt form, e.g. HCl salt form, and (LI) are reacted with paraformaldehyde in the presence of a suitable solvent, such as for example an alcohol, e.g. ethanol, then a suitable agent P—O—P to introduce a suitable protective group P, such as for example C(═O)—O—C(CH_3)$_3$ wherein P—O—P is (CH_3)$_3$C—O—C(═O)—OC(═O)—O—C(CH_3)$_3$), is added in the presence of a suitable base, such as for example triethylamine, and a suitable solvent, such as for example dichloromethane, resulting in an intermediate of formula (LVI), which is further reacted with p-toluenesulfonhydrazide in the presence of a suitable solvent, such as for example an alcohol, e.g. ethanol, to give an intermediate of formula (LVII). The intermediate of formula (LVII) is then further reacted with an intermediate of formula (XLVII) in the presence of a suitable catalyst, such as for example tris (dibenzylideneacetone)dipalladium (0), a suitable ligand, such as for example 2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl a suitable base, such as for example lithium tert-butoxide, and a suitable solvent, such as for example dioxane, resulting in an intermediate of formula (LVIII), the E and Z isomers of which can be separated by appropriate separation techniques such as column chromatography. The intermediate of formula (LVIII) can then be converted into a compound of formula (Ie-4) by deprotection in the presence of a suitable acid, such as for example HCl, and a suitable solvent, such as for example an alcohol, e.g. methanol. A compound of formula (Ie-5) is prepared by reacting an intermediate of formula (LX) with p-toluenesulfonhydrazide in the presence of a suitable acid, such as for example hydrochloric acid, and a suitable solvent, such as for example diethylether and water, resulting in an intermediate of formula (LIX), the E and Z isomers of which can be separated by appropriate separation techniques such as column chromatography. The intermediate of formula (LIX) can then be reacted with an intermediate of formula (XLVII) in the presence of a suitable catalyst, such as for example tris(dibenzylideneacetone)dipalladium (0), a suitable ligand, such as for example 2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl a suitable base, such as for example lithium tert-butoxide, and a suitable solvent, such as for example dioxane, resulting in a compound of formula (Ie-5). A compound of formula (Ie-6) is prepared by reacting an intermediate of formula (LXI) with a suitable reducing agent, such as for example diisobutylaluminium hydride, and a suitable solvent, such as for example tetrahydrofuran. The intermediate of formula (LXI) is prepared by reacting an intermediate of formula (XLVII) with an intermediate of formula (LXII) in the presence of a suitable catalyst, such as for example palladium(II)acetate, a suitable ligand, such as for example tri-o-tolylphosphine, a suitable base, such as for example triethylamine, and a suitable solvent, such as for example acetonitrile. Intermediates of formula (LXI) can also be prepared by reacting a compound of formula (Ie-1) with triethylphosphonoacetate in the presence of a suitable base, such as for example sodium hydride, and a suitable solvent, such as for example tetrahydrofuran.

Compounds of formula (Ie) can also be prepared according to the following reaction Scheme 14.

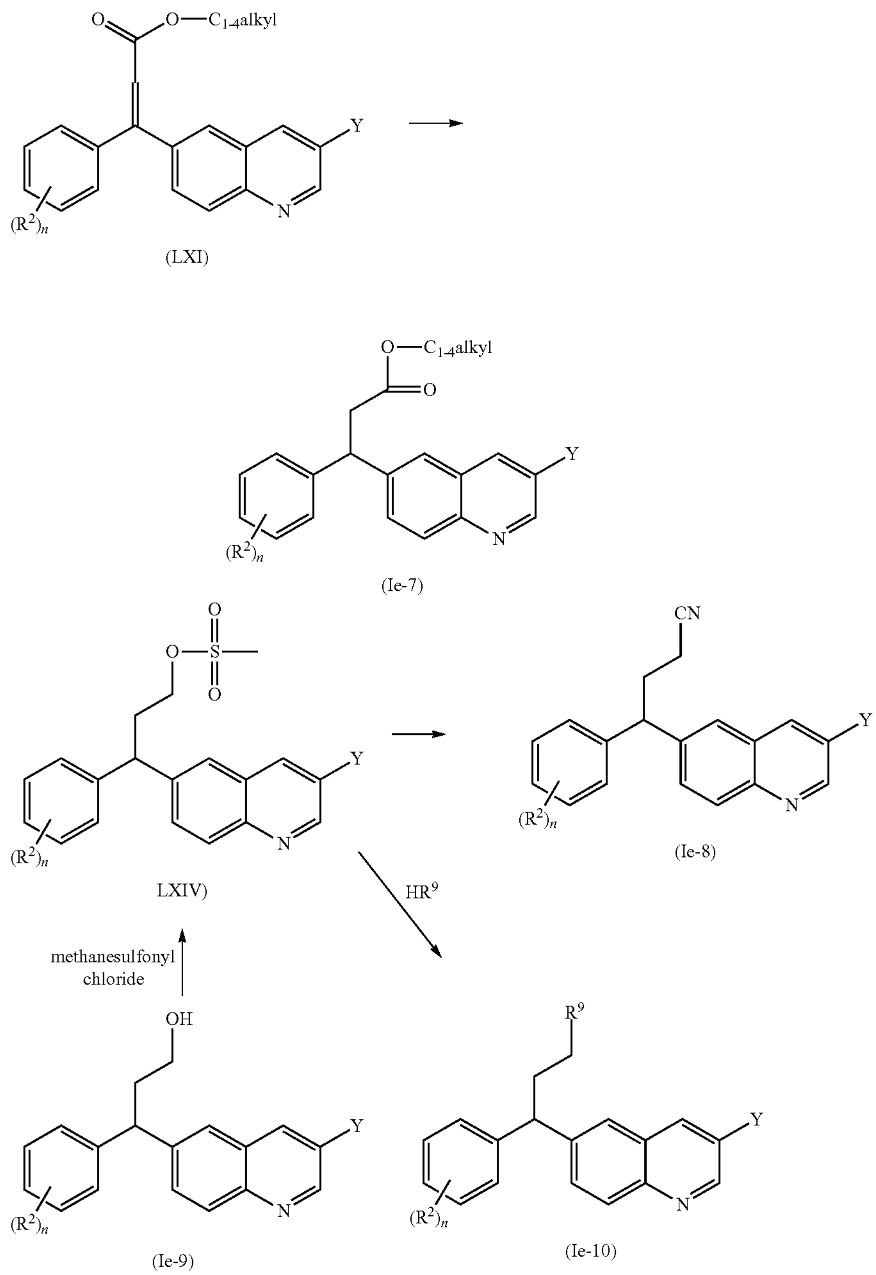
Scheme 14



In Scheme 14, a compound of formula (Ie-6) is reacted with a leaving group introducing agent, such as for example methanesulfonyl chloride, in the presence of a suitable base, such as for example triethylamine, and a suitable solvent, such as for example dichloromethane, resulting in an an intermediate of formula (LXIII) wherein W_{17} represents a suitable leaving group, such as for example halo, e.g. chloro, which is then further reacted with NHR^{11} in the presence of a suitable solvent, such as for example acetonitrile, to give a compound of formula (Ie-4).

Compounds of formula (Ie) can also be prepared according to the following reaction Scheme 15.

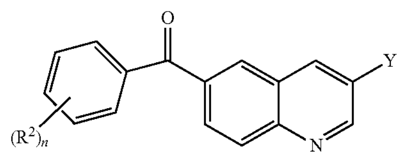
Scheme 15



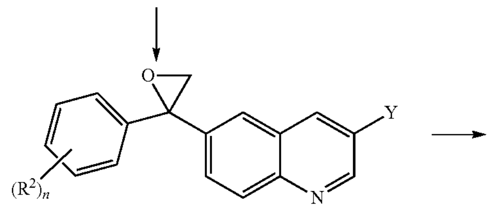
In Scheme 15, a compound of formula (Ie-7) is prepared by reacting an intermediate of formula (LXI) with magnesium in the presence of a suitable solvent, such as for example tetrahydrofuran and an alcohol, e.g. methanol and the like. A compound of formula (Ie-8) is prepared by reacting an intermediate of formula (LXIV) with potassium cyanide in the presence of a suitable solvent, such as for example N,N-dimethylformamide. The intermediate of formula (LXIV) is prepared by reacting a compound of formula (Ie-9) with methanesulfonyl chloride in the presence of a suitable base, such as for example triethylamine, and a suitable solvent, such as for example acetonitrile. (Ie-9) can be prepared by reduction of (Ie-6) for example using $LiAlH_4$, in an aprotic solvent such as THF. The intermediate of formula (LXIV) is converted into a compound of formula (Ie-10) by reaction with HR^9 in the presence of a suitable base, such as for example sodium hydride, and a suitable solvent, such as for example N,N-dimethylformamide. Compounds of formula (Ie-7) can also be prepared by reacting a compound of formula (Ie-9) with lithiumaluminiumhydride in the presence of a suitable solvent, such as for example tetrahydrofuran.

Compounds of formula (Ie) can also be prepared according to the following reaction Scheme 16.

Scheme 16



(Ie-1)



(LXV)

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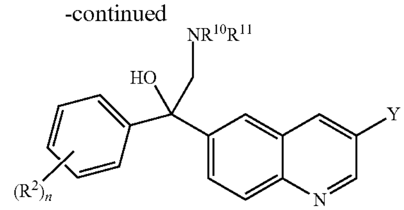
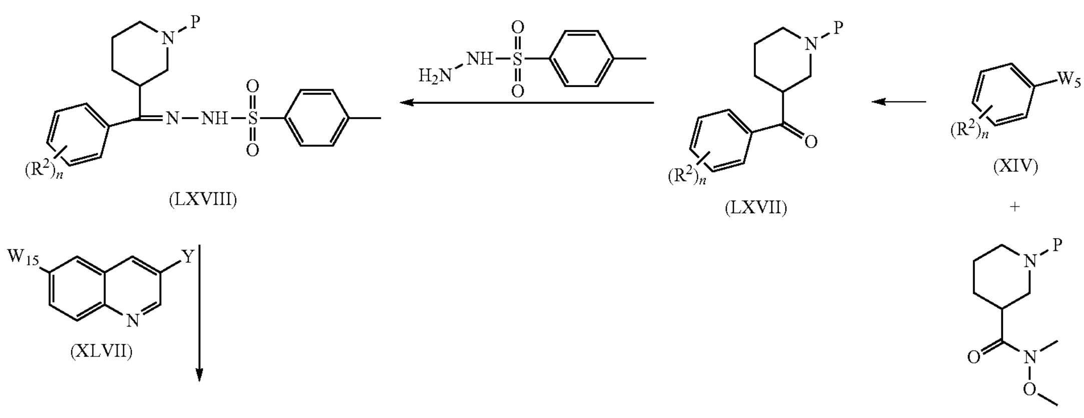


(Ie-11)

In Scheme 16, a compound of formula (Ie-1) is reacted with trimethylsulphoxonium iodide in the presence of a suitable base, such as for example potassium tert butoxide, and a suitable solvent, such as for example dimethoxymethane and dimethylsulfoxide resulting in an intermediate of formula (LXV), which can be converted into a compound of formula (Ie-11) by reaction with $NHR^{10}R^{11}$ in the presence of a suitable solvent, such as for example an alcohol, e.g. ethanol and the like.

Compounds of formula (Ie) can also be prepared according to the following reaction Scheme 17.

Scheme 17



(LXVIII)

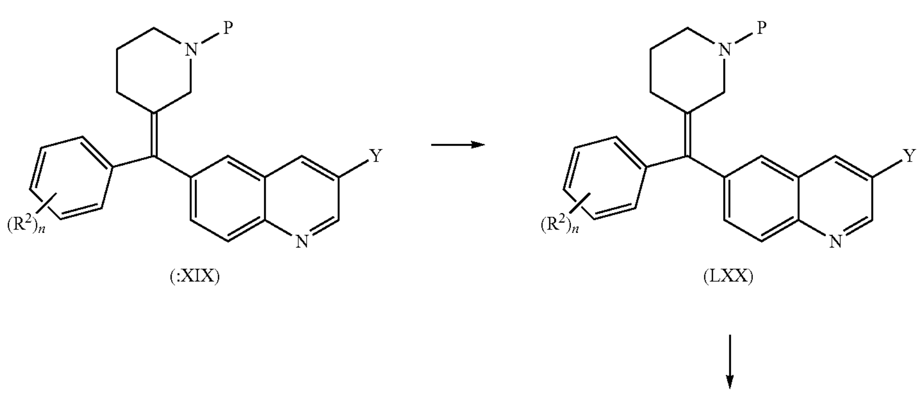
(XLVII)

(LXVII)

(XIV)

+

(LXVI)



(:XIX)

(LXX)

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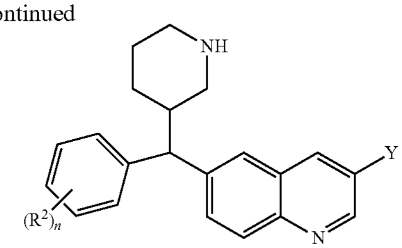
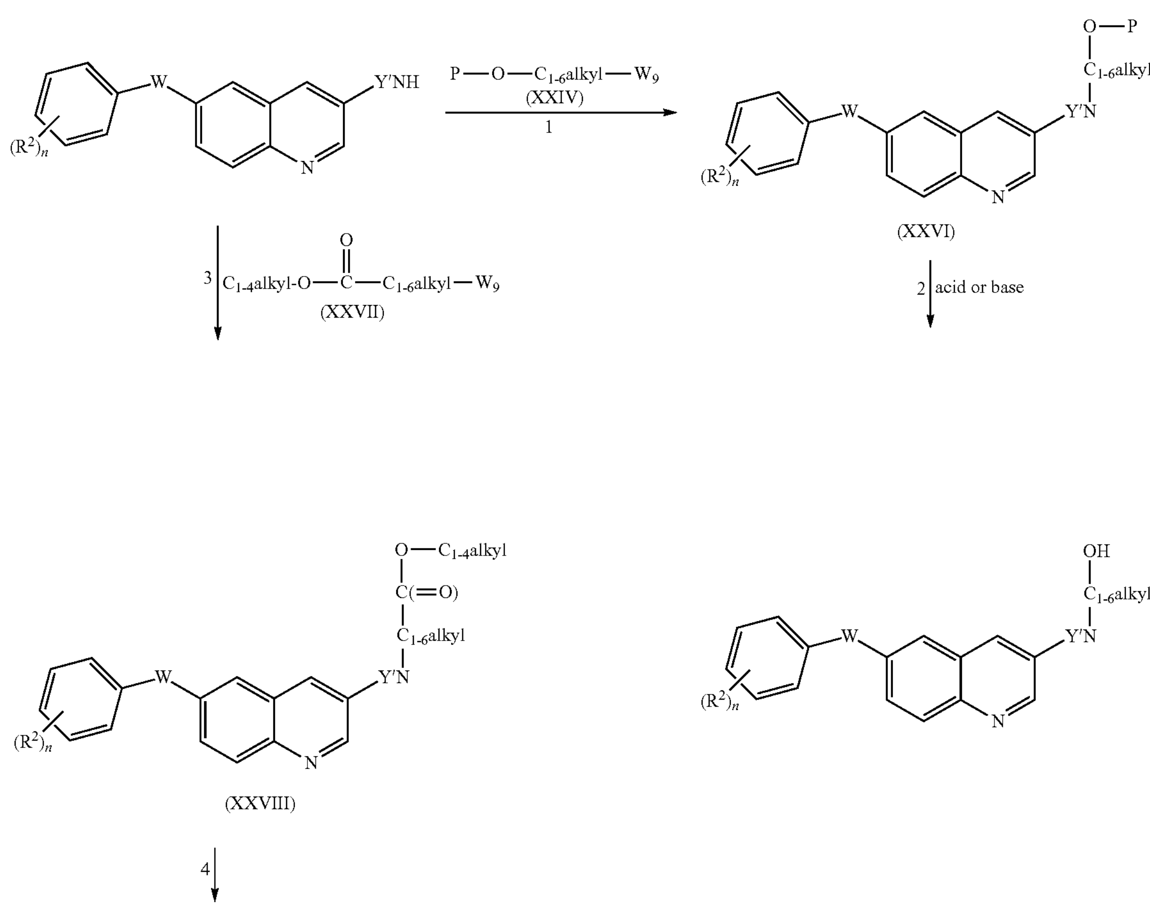


(Ie-12)

In Scheme 17, an intermediate of formula (XIV) as defined above, and (LXVI) wherein P represents a suitable protective group as defined above, is reacted with butyllithium in hexane in the presence of a suitable solvent, such as for example tetrahydrofuran, diethylether or mixtures thereof resulting in an intermediate of formula (LXVII), which is further reacted with p-toluenesulfonhydrazide in the presence of a suitable solvent, such as for example an alcohol, e.g. ethanol, to give an intermediate of formula (LXVIII). The intermediate of formula (LXVIII) is then further reacted with an intermediate of formula (XLVII) in the presence of a suitable catalyst, such as for example tris(dibenzylideneacetone)dipalladium (0), a suitable ligand, such as for example 2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl, a suitable base, such as for example lithium tert-butoxide, and a suitable solvent, such as for example dioxane, resulting in an intermediate of formula (LXIX). The intermediate of formula (LXIX) is then converted into an intermediate of formula (LXX) by hydrogenation in the presence of a suitable catalyst, such as for example palladium on charcoal, and a suitable solvent, such as for example an alcohol, e.g. methanol. The intermediate of formula (LXX) can then be converted into a compound of formula (Ie-12) by reaction with a suitable acid, such as for example hydrochloric acid, in the presence of a suitable solvent, such as for example an alcohol, e.g. methanol.

As already shown above, compounds of formula (I) or some of the above-described intermediates can be prepared by deprotecting the corresponding protected compounds. Other protection-deprotection reactions are shown in the following reaction Scheme 18.

Scheme 18



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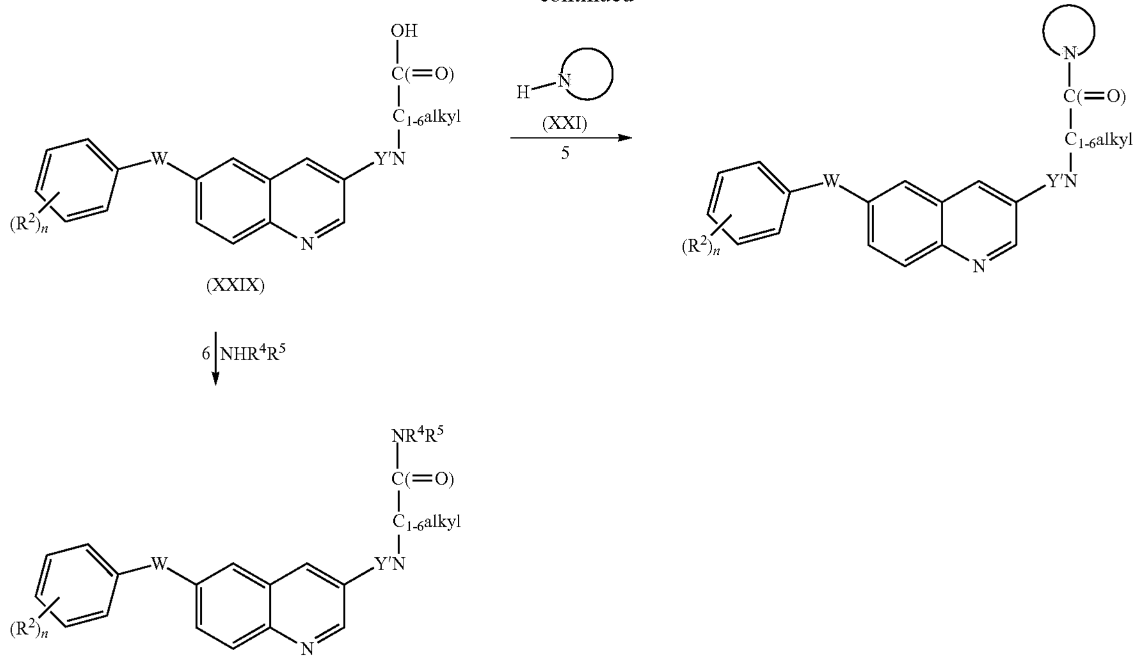
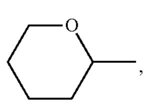


In Scheme 18, the Y'N moiety represents an -E-D moiety wherein the D ring moiety contains a nitrogen atom. Compounds of formula (I) wherein R^1 represents hydroxyC_{1-6}alkyl can be prepared by deprotecting an intermediate of formula (XXVI) in the presence of a suitable acid, such as for example HCl or trifluoroacetic acid, or a suitable desilylating agent, such as for example tetrabutyl ammonium fluoride, and a suitable solvent, such as an alcohol, e.g. methanol, or tetrahydrofuran (step 2). Intermediates of formula (XXVI) can be prepared by reacting a compound of formula (I) wherein R^1 is hydrogen with an intermediate of formula (XXIV) wherein W_9 represents a suitable leaving group, such as for example halo, e.g. bromo and the like, and P represents a suitable protective group, such as for example —$Si(CH_3)_2(C(CH_3)_3)$ or

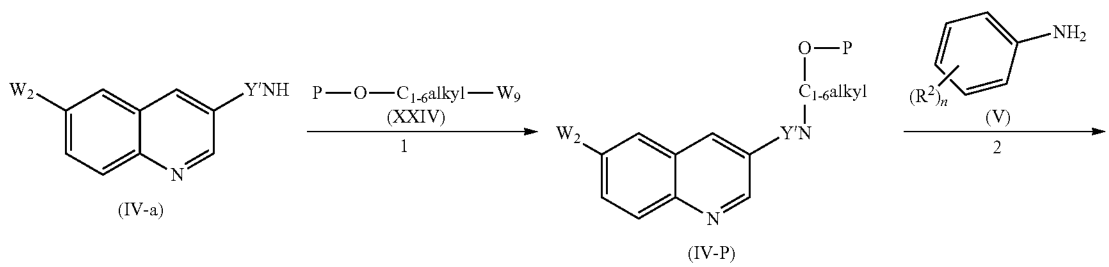


in the presence of a suitable base, such as for example sodium hydride or K_2CO_3, and a suitable solvent, such as for example N,N-dimethylformamide or acetonitrile (step 1). Compounds of formula (I) wherein R^1 represents C_{1-6}alkyl substituted with —C(═O)—R^6 wherein R^6 is an appropriate nitrogen containing ring linked to the C(═O) moiety via the nitrogen atom can be prepared by reacting an intermediate of formula (XXIX) with an intermediate of formula (XXI) in the presence of suitable peptide coupling reagents such as, 1-hydroxy-benzotriazole and 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide HCl (step 5). Intermediates of formula (XXIX) can be prepared by reacting an intermediate of formula (XXVIII) with LiOH in the presence of a suitable solvent, such as for example tetrahydrofuran or water (step 4). Intermediates of formula (XXVIII) can be prepared by as depicted in step 3 with an intermediate of formula (XXVII) wherein W_9 is as defined above, in the presence of a suitable base, such as for example sodium hydride, and a suitable solvent, such as for example N,N-dimethylformamide.

Step 6 depicts the preparation of compounds of formula (I) starting from an intermediate of formula (XXIX) by reaction with NHR^4R^5 in the presence of suitable peptide coupling reagents such as 1-hydroxy-benzotriazole and 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide HCl and a suitable base, such as triethylamine, and a suitable solvent, such as for example dichloromethane.

Further protection-deprotection reactions can also be used as outlined in the following reaction Scheme 19.

Scheme 19



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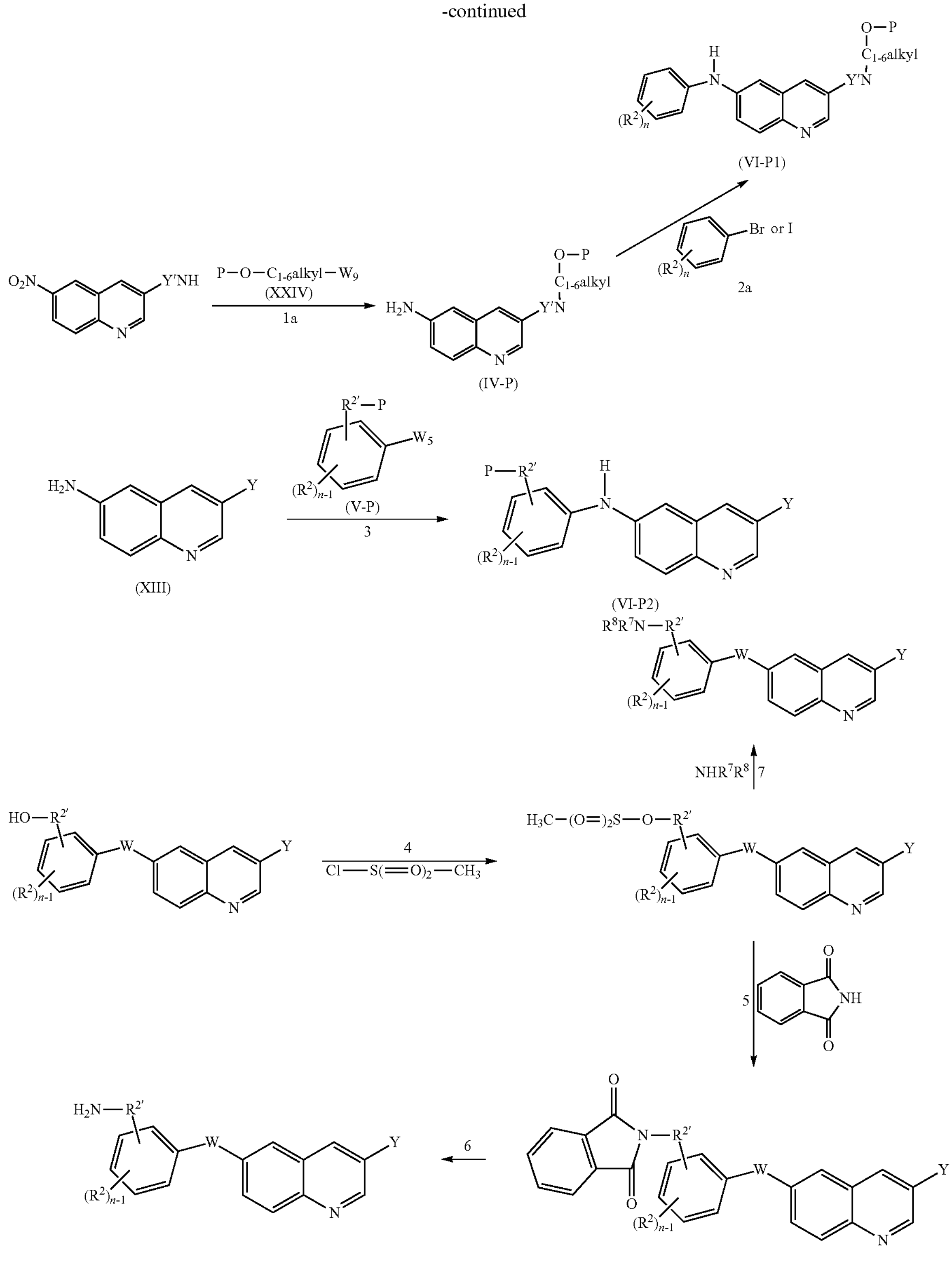


In Scheme 19, the following reaction conditions apply:

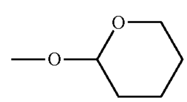
1; in the presence of a suitable base, such as for example sodium hydride, and a suitable solvent, such as for example N,N-dimethylformamide.

2: in the presence of a suitable catalyst, such as for example palladium (II)acetate, a suitable base, such as for example sodium tert-butoxide, a suitable ligand, such as for example 1,1'-[1,1'-binaphthalene]-2,2'-diylbis[1,1-diphenylphosphine], and a suitable solvent, such as for example dioxane or ethylene glycol dimethylether.

1a; in the presence of a suitable base, such as for example sodium hydride, and a suitable solvent, such as for example N,N-dimethylformamide, followed by reduction with H_2 and Raney nickel, in a suitable alcohol,

2a: in the presence of a suitable catalyst, such as for example palladium (II)acetate, a suitable base, such as for example sodium tert-butoxide, a suitable ligand, such as for example 1,1'-[1,1'-binaphthalene]-2,2'-diylbis[1,1-diphenylphosphine], and a suitable solvent, such as for example dioxane or ethylene glycol dimethylether.
3: in the presence of a suitable catalyst, such as for example palladium (II)acetate, a suitable base, such as for example sodium tert-butoxide, a suitable ligand, such as for example 1,1'-[1,1'-binaphthalene]-2,2'-diylbis[1,1-diphenylphosphine], and a suitable solvent, such as for example dioxane or ethylene glycol dimethylether.
4: in the presence of a suitable base, such as for example triethylamine, and a suitable solvent, such as for example dichloromethane.
5: in the presence of a suitable base, such as for example K_2CO_3, and a suitable solvent, such as for example 1-methyl-2-pyrrolidinone.
6: in the presence of hydrazine monohydrate, and a suitable solvent, such as for example an alcohol, e.g. ethanol.
7: in the presence of a suitable base, such as for example K_2CO_3, and a suitable solvent, such as for example tetrahydrofuran.

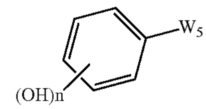
It is considered to be within the knowledge of the person skilled in the art to recognize in which condition and on which part of the molecule a protective group may be appropriate. For instance, protective group on the R^1 substituent or on the D moiety, or protective group on the R^3 substituent or on the R^2 substituent or combinations thereof. The skilled person is also considered to be able to recognize the most feasible protective group, such as for example —C(═O)—O—C_{1-4}alkyl or



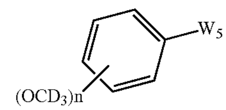
or O—$Si(CH_3)_2(C(CH_3)_3)$ or —CH_2—O—CH_2CH_2—O—CH_3 or —CH_2—O—CH_2—CH_2—$Si(CH_3)_3$. The skilled person is also considered to be able to recognize the most feasible deprotection reaction conditions, such as for example suitable acids, e.g. trifluoroacetic acid, hydrochloric acid, or suitable salts, such as for example tetrabutylammonium fluoride. Reference herefore is also made to the examples described in the Experimental Part hereinafter.

The skilled person is also considered to be able to recognize that when R^1 represents C(═O)-morpholinyl, said R^1 can be prepared from C(═O)—NH—CH_2—CH_2—O—CH_2—CH_2—O—SO_2-4-methylphenyl, in the presence of sodium hydride, and a suitable solvent, such as for example N,N-dimethylformamide. Or that when R^1 represents NH—C(═O)-morpholinyl, said R^1 can be prepared from NH—C(═O)—O—$C(CH_3)_3$ in the presence of morpholine, and a suitable solvent, such as for example 1-methyl-2-pyrrolidinone. Or that when R^1 represents hydroxylC_{1-6}alkyl, e.g. —CH_2—CH_2—OH, said R^1 can be prepared from the corresponding alkoxycarbonyl intermediate, e.g. —CH_2—C(═O)—O—CH_2—CH_3, in the presence of Dibal-H 1M in hexane, and a suitable solvent, such as for example tetrahydrofuran.

The present invention also comprises deuterated compounds. These deuterated compounds may be prepared by using the appropriate deuterated intermediates during the synthesis process. For instance an intermediate of formula (IV-a)



can be converted into an intermediate of formula (IV-b)



by reaction with iodomethane-D3 in the presence of a suitable base, such as for example cesium carbonate, and a suitable solvent, such as for example acetonitrile.

The compounds of formula (I) may also be converted into each other via art-known reactions or functional group transformations.

For instance, compounds of formula (I) wherein R^1 represents tetrahydropyranyl can be converted into a compound of formula (I) wherein R^1 represents hydrogen, by reaction with a suitable acid, such as for example HCl or trifluoroacetic acid, in the presence of a suitable solvent, such as for example dichloromethane, dioxane, or an alcohol, e.g. methanol, isopropanol and the like.

Compounds of formula (I) wherein R^1 or R^3 represent monohaloalkyl, can be converted into a compound of formula (I) wherein R^1 or R^3 represent C_{1-6}alkyl substituted with a ring moiety as defined hereinabove by the intermediate of formula (XXI) and linked to the C_{1-6}alkyl moiety by the nitrogen atom, by reaction with an intermediate of formula (XXI) optionally in the presence of a suitable base, such as for example triethylamine or K_2CO_3 or sodium hydride, and optionally in the presence of a suitable solvent, such as for example acetonitrile, N,N-dimethylformamide or 1-methyl-2-pyrrolidinone.

Compounds of formula (I) wherein R^1 or R^3 represents C_{1-6}alkyl-OH, can be converted into a compound of formula (I) wherein R^1 or R^3 represent C_{1-6}alkyl-F by reaction with diethylaminosulfur trifluoride in the presence of a suitable solvent, such as for example dichloromethane and in the presence of catalytic amounts of an alcohol, such as for example ethanol. Likewise, a compound of formula (I) wherein R^1 or R^3 represent C_{1-6}alkyl substituted with R^6 or R^9 wherein said R^6 or R^9 is substituted with OH, can be converted into a compound of formula (I) wherein R^1 or R^3 represent C_{1-6}alkyl substituted with R^6 or R^9 wherein said R^6 or R^9 is substituted with F, by reaction with diethylaminosulfur trifluoride in the presence of a suitable solvent, such as for example dichloromethane.

Compounds of formula (I) wherein R^1 or R^3 represent C_{1-6}alkyl substituted with R^6 or R^9 wherein said R^6 or R^9 is substituted with —C(═O)—O—C_{1-6}alkyl, can be converted into a compound of formula (I) wherein R^1 or R^3 represent C_{1-6}alkyl substituted with R^6 or R^9 wherein said R^6 or R^9 is substituted with —CH_2—OH, by reaction with $LiAlH_4$ in the presence of a suitable solvent, such as for example tetrahydrofuran.

Compounds of formula (I) wherein R^3 represents C_{1-6}alkyl substituted with 1,3-dioxo-2H-isoindol-2-yl, can be converted into a compound of formula (I) wherein R^3 represents C_{1-6}alkyl substituted with amino, by reaction with hydrazine monohydrate in the presence of a suitable solvent, such as for example an alcohol, e.g. ethanol.

Compounds of formula (I) wherein R^1 or R^3 represent C_{1-6}alkyl substituted with amino, can be converted into a compound of formula (I) wherein R^1 or R^3 represents C_{1-6}alkyl substituted with —NH—S(═O)$_2$—C_{1-6}alkyl, by reaction with Cl—S(═O)$_2$—C_{1-6}alkyl in the presence of a suitable base, such as for example triethylamine, and a suitable solvent, such as for example dichloromethane.

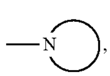
Compounds of formula (I) wherein R^1 or R^3 represents C_{1-6}alkyl substituted with halo, can be converted into a compound of formula (I) wherein R^1 or R^3 represent C_{1-6}alkyl substituted with NR^4R^5 or $NR^{10}R^{11}$, by reaction with NHR^4R^5 or $NHR^{10}R^{11}$, either using such amino in large excess or in the presence of a suitable base, such as for example K_2CO_3, and a suitable solvent, such as for example acetonitrile, N,N-dimethylacetamide or 1-methyl-pyrrolidinone.

Compounds of formula (I) wherein R^1 represents hydrogen, can be converted into a compound of formula (I) wherein R^1 represents polyhaloC_{1-6}alkyl or polyhydroxy-C_{1-6}alkyl or C_{1-6}alkyl or —S(═O)$_2$—$NR^{14}R^{15}$ or —S(═O)$_2$—C_{1-6}alkyl, by reaction with polyhalo-C_{1-6}alkyl-W or polyhydroxyC_{1-6}alkyl-W or C_{1-6}alkyl-W or W—S(═O)$_2$—$NR^{14}R^{15}$ or W—S(═O)$_2$—C_{1-6}alkyl, wherein W represents a suitable leaving group, such as for example halo, e.g. bromo and the like, in the presence of a suitable base, such as for example sodium hydride or K_2CO_3 or triethylamine or 4-dimethylamino-pyridine or diisopropylamine, and a suitable solvent, such as for example N,N-dimethylformamide or acetonitrile or dichloromethane.

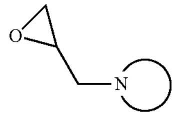
Compounds of formula (I) wherein R^1 represents hydrogen can also be converted into a compound of formula (I) wherein R^1 represents C_{1-6}alkyl-OH, by reaction with W—C_{1-6}alkyl-O—$Si(CH_3)_2(C(CH_3)_3)$ in the presence of a suitable base, such as for example sodium hydride, and a suitable solvent, such as for example N,N-dimethylformamide and, then followed by a reaction with a suitable desilylating agent such as tetrabutyl ammonium fluoride.

Compounds of formula (I) wherein R^1 represents hydrogen, can also be converted into compound of formula (I) wherein R^1 represents ethyl substituted with S(═O)$_2$—C_{1-6}alkyl, by reaction with C_{1-6}alkyl-vinylsulfone, in the presence of a suitable base, such as for example triethylamine, and a suitable solvent, such as for example an alcohol, e.g. methanol or by reaction with C_{1-6}alkyl-2-bromoethylsulfone in the presence of a suitable deprotonating agent, such as for example NaH, and a suitable solvent, such as for example dimethylormamide.

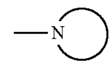
Compounds of formula (I) wherein R^1 represents hydrogen can also be converted into a compound of formula (I) wherein R^1 represents —CH_2—CHOH—CH_2



by reaction with



in the presence of a suitable base, such as for example sodium hydride, and a suitable solvent, such as for example N,N-dimethylformamide, wherein



represents a suitable nitrogen containing ring within the definition of R^6.

Compounds of formula (I) wherein R^1 represents C_{1-6}alkyl substituted with R^6 wherein said R^6 is substituted with —C(═O)—O—C_{1-6}alkyl or —S(═O)$_2$—$NR^{14}R^{15}$ or wherein R^3 represents C_{1-6}alkyl substituted with R^9 wherein said R^9 is substituted with —C(═O)—O—C_{1-6}alkyl or —S(═O)$_2$—$NR^{14}R^{15}$, can be converted into a compound of formula (I) wherein the R^6 or R^9 is unsubstituted, by reaction with a suitable acid, such as for example HCl and a suitable solvent, such as for example dioxane, acetonitrile or an alcohol, e.g. isopropylalcohol. Compounds of formula (I) wherein R^1 represents C_{1-6}alkyl substituted with R^6 wherein said R^6 is a ring moiety comprising a nitrogen atom which is substituted with —CH_2—OH or wherein R^3 represents C_{1-6}alkyl substituted with R^9 wherein said R^9 is a ring moiety comprising a nitrogen atom which is substituted with —CH_2—OH, can be converted into a compound of formula (I) wherein the R^6 or R^9 is unsubstituted, by reaction with sodium hydroxide, in the presence of a suitable solvent, such as for example tetrahydrofuran.

Compounds of formula (I) wherein R^1 represents C_{1-6}alkyl substituted with R^6 or R^3 represents C_{1-6}alkyl substituted with R^9, wherein said R^6 or said R^9 is unsubstituted, can be converted into a compound of formula (I) wherein said R^6 or said R^9 is substituted with C_{1-6}alkyl, by reaction with W—C_{1-6}alkyl wherein W is as defined above, in the presence of a suitable base. Such as for example sodium hydride, and a suitable solvent, such as for example N,N-dimethylformamide.

Compounds of formula (I) wherein R^1 or R^3 represent hydroxyC_{1-6}alkyl, can be converted into the corresponding carbonyl compound, by reaction with dess-Martin-periodinane, in the presence of a suitable solvent, such as for example dichloromethane.

Compounds of formula (I) wherein R^1 represents C_{1-6}alkyl substituted with R^6 or R^3 represents C_{1-6}alkyl substituted with R^9, wherein said R^6 or said R^9 is substituted with C_{1-6}alkyl-halo, can be converted into a compound of formula (I) wherein said R^6 or said R^9 is substituted with C_{1-6}alkyl-CN, by reaction with sodium cyanide, in the presence of a suitable solvent, such as for example water or an alcohol, e.g. ethanol.

Compounds of formula (I) wherein R^1 represents C_{1-6}alkyl substituted with R^6 wherein said R^6 is unsubstituted or wherein R^3 represents C_{1-6}alkyl substituted with R^9 wherein said R^9 is unsubstituted, can be converted into a compound of formula (I) wherein R^6 or R^9 is substituted with —CH_3 or —$CH(CH_3)_2$, by reaction with formaldehyde or acetone and $NaBH_3CN$, in the presence of a suitable solvent, such as for example tetrahydrofuran or an alcohol, e.g. methanol.

Compounds of formula (I) wherein R^1 contains a R^6 substituent substituted with OH or wherein R^3 contains a R^9 substituent substituted with OH, can be converted into a compound of formula (I) wherein the R^6 or R^9 substituent is substituted with C_{1-6}alkyloxy, by reaction with W—C_{1-6}alkyl, in the presence of a suitable base, such as for example sodium hydride, and a suitable solvent, such as for example N,N-dimethylformamide.

Compounds of formula (I) wherein R^1 contains a R^6 substituent substituted with C_{1-6}alkyloxy or wherein R^3 contains a R^9 substituent substituted with C_{1-6}alkyloxy, can be converted into a compound of formula (I) wherein the R^6 or R^9 substituent is substituted with OH by reaction with a suitable acid, such as for example hydrochloric acid.

Compounds of formula (I) wherein R^1 contains a R^6 substituent substituted with halo or wherein R^3 contains a R^9 substituent substituted with halo can be converted into a compound of formula (I) wherein the R^6 or R^9 substituent is substituted with —$NR^{14}R^{15}$ by reaction with $NHR^{14}R^{15}$ in a suitable sovent, such as for example 1-methyl-pyrrolidinone.

Compounds of formula (I) wherein R^3 represents C_{1-6}alkyl substituted with —C(═O)—O—C_{1-6}alkyl, can be converted into a compound of formula (I) wherein R^3 represents C_{1-6}alkyl substituted with COOH, by reaction with LiOH in the presence of a suitable solvent, such as for example tetrahydrofuran. Said compounds of formula (I) wherein R^3 represents C_{1-6}alkyl substituted with COOH, can be converted into a compound of formula (I) wherein R^3 represents C_{1-6}alkyl substituted with —C(═O)—NH_2 or —C(═O)—$NHCH_3$ or —C(═O)$NR^{10}R^{11}$, by reaction with $NH(Si(CH_3)_3)_2$ or $MeNH_3^+Cl^-$ or $NHR^{10}R^{11}$ in the presence of suitable peptide coupling reagents such as for example 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide HCl and 1-hydroxybenzotriazole, a suitable base, such as for example triethylamine and a suitable solvent such as for example dichloromethane or N,N-dimethylformamide. Compounds of formula (I) wherein R^3 represents C_{1-6}alkyl substituted with —C(═O)—O—C_{1-6}alkyl, can also be converted into a compound of formula (I) wherein R^3 represents C_{1-6}alkyl substituted with 4,5-dihydro-1H-imidazolyl, by reaction under N_2 with ethylenediamine and trimethylaluminium in the presence of a suitable solvent, such as for example toluene and heptane. Compounds of formula (I) wherein R^3 represents C_{1-6}alkyl substituted with COOH, can also be converted into a compound of formula (I) wherein R^3 represents C_{1-6}alkyl substituted with —C(═O)—$N(CH_3)(OCH_3)$ by reaction with dimethylhydroxylamine, in the presence of carbonyldiimidazole and a suitable solvent, such as for example dichloromethane.

Compounds of formula (I) wherein R^3 represents C_{1-6}alkyl substituted with

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can be converted into a compound of formula (I) wherein R^3 represents C_{1-6}alkyl substituted with 2OH's, by reaction with a suitable acid, such as for example trifluoroacetic acid, and a suitable solvent, such as for example dioxane or water. These compounds of formula (I) wherein R^3 represents C_{1-6}alkyl substituted with

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can also be converted into a compound of formula (I) wherein R^3 represents C_{1-6}alkyl substituted with OH and $NR^{10}R^{11}$, by reaction with $NH_2R^{10}R^{11}$ optionally in salt form, such as for example $NHR^{10}R^{11+}Cl^-$, optionally in the presence of a suitable base, such as for example sodium hydride or Na_2CO_3 or triethylamine, a suitable additive such as for example KI, and in the presence of a suitable solvent, such as for example N,N-dimethylformamide or an alcohol, e.g. 1-butanol or ethanol.

Compounds of formula (I) wherein R^3 represents C_{1-3}alkyl substituted with —C(═O)—O—C_{1-6}alkyl, can be converted into a compound of formula (I) wherein R^3 represents C_{1-3}alkyl substituted with —C(CH3)$_2$—OH, by reaction with iodomethane and Mg powder, in the presence of a suitable solvent, such as for example diethylether or tetrahydrofuran.

Compounds of formula (I) wherein R^3 represents C_{1-5}alkyl substituted with —C(═O)—O—C_{1-6}alkyl, can be converted into a compound of formula (I) wherein R^3 represents C_{1-6}alkyl substituted with —OH, by reaction with $LiAlH_4$ in a suitable solvent, such as for example tetrahydrofuran.

Compounds of formula (I) wherein R^3 represents C_{1-6}alkyl substituted with OH, can be converted into a compound of formula (I) wherein R^3 represents C_{1-5}alkyl substituted with —O—C(═O)—C_{1-6}alkyl by reaction with Cl—C(═O)—C_{1-6}alkyl in the presence of a suitable base, such as for example NaH, and a suitable solvent, such as for example tetrahydrofuran.

Compounds of formula (I) wherein R^3 represents —CH_2—CH═CH_2, can be converted into a compound of formula (I) wherein R^3 represents —CH_2—CHOH—CH_2—OH, by reaction with potassium permanganate, and a suitable solvent, such as for example acetone or water.

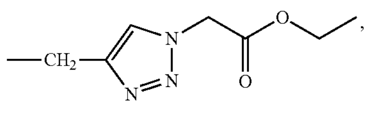
Compounds of formula (I) wherein R^3 represents C_{1-6}alkyl substituted with —C(═O)—C_{1-4}alkyl, can be converted into a compound of formula (I) wherein R^3 represents C_{1-6}alkyl substituted with C(C_{1-4}alkyl)═N—OH, by reaction with hydroxylamine, in the presence of a suitable base, such as for example pyridine, and a suitable solvent, such as for example an alcohol, e.g. ethanol.

Compounds of formula (I) wherein R^3 represents C_{1-6}alkyl substituted with NH_2, can be converted into a compound of formula (I) wherein R^3 represents C_{1-6}alkyl substituted with —NH—C(═O)—R^6 or with —NH—C(═O)—C_{1-6}alkyl or with —NH—C(═O)-polyhydroxy-C_{1-6}alkyl or with —NH—C(═O)-polyhaloC_{1-6}alkyl or with —NH—C(═O)-polyhydroxypolyhaloC_{1-6}alkyl, by reaction with the corresponding COOH analogue, e.g. R^6—COOH or CF_3—C(CH_3)(OH)—COOH and the like, in the presence of suitable peptide coupling reagents such as 1-hydroxy-benzotriazole and 1-(3-dimethylamino)propyl) carbodiimide optionally in the presence of a suitable base, such as for example triethylamine. Said compounds of formula (I) wherein R^3 represents C_{1-6}alkyl substituted with NH_2, can also be converted into a compound of formula (I) wherein R^3 represents C_{1-6}alkyl substituted with NH—C(═O)—CF_3, by reaction with trifluoroacetic anhydride, in the presence of a suitable base, such as for example triethylamine, and a suitable solvent, such as for example tetrahydrofuran. Said compounds of formula (I) wherein R^3 represents C_{1-6}alkyl substituted with NH_2, can also be converted into a compound of formula (I) wherein R^3 represents C_{1-6}alkyl substituted with —NH-polyhalo-C_{1-6}alkyl, e.g. NH—CH_2—CH_2—F, by reaction with polyhaloC_{1-6}alkyl-W, with W as defined above, e.g. iodo-2-fluoroethane, in the presence of a suitable base, such as for example K_2CO_3, and a suitable solvent, such as for example N,N-dimethylformamide or dioxane. Said compounds of formula (I) wherein R^3 represents C_{1-6}alkyl substituted with

NH_2 can also be converted into a compound of formula (I) wherein R^3 represents C_{1-6}alkyl substituted with —NH—R^6 or —N(R^6)$_2$ wherein R^6 represents for example oxetane, by reaction with the appropriate R^6 in the presence of a suitable reducing agent, such as for example sodium triacetoxyborohydride, a suitable acid, such as for example acetic acid, and a suitable solvent, such as for example 1,2-dichloroethane.

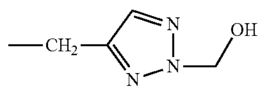
Compounds of formula (I) wherein R^3 represents C_{1-6}alkyl substituted with cyano, can be converted into a compound of formula (I) wherein R^3 represents C_{1-6}alkyl substituted with tetrazolyl by reaction with sodium azide, and $NH_4^+Cl^-$ in the presence of a suitable solvent, such as for example N,N-dimethylformamide.

Compounds of formula (I) wherein R^3 represents —CH2-C≡CH, can be converted into a compound of formula (I) wherein R^3 represents



by reaction with ethyl azidoacetate in the presence of CuI and a suitable base, such as for example diisopropylamine, and a suitable solvent, such as for example tetraydrofuran.

Compounds of formula (I) wherein R^3 represents —CH2-C≡CH, can be converted into a compound of formula (I) wherein R^3 represents



by reaction with sodium azide and formaldehyde, in the presence of a suitable catalyst, such as for example $CuSO_4$ and sodium L ascorbate, a suitable acid, such as for example acetic acid, and a suitable solvent, such as for example dioxane.

Compounds of formula (I) wherein R^3 represent C_{2-6}alkynyl, can be converted into a compound of formula (I) wherein R^3 represents C_{2-6}alkynyl substituted with R^9, by reaction with W—R^9 wherein W is as defined above, in the presence of a suitable catalyst, such as for example dichlorobis(triphenylphosphine)palladium, a suitable co-catalyst such as CuI, a suitable base, such as for example triethylamine, and a suitable solvent, such as for example dimethylsulfoxide.

Compounds of formula (I) wherein R^3 comprises R^9 substituted with halo, can be converted into a compound of formula (I) wherein R^3 comprises R^9 substituted with —$NR^{14}R^{15}$ (by reaction with $NHR^{14}R^{15}$ in the presence of a suitable solvent, such as for example 1-methyl-2-pyrrolidinone.

Compounds of formula (I) wherein R^3 comprises C_{2-6}alkynyl, can be hydrogenated into a compound of formula (I) wherein R^3 comprises C_{2-6}alkyl in the presence of a suitable catalyst, such as for example palladium on charcoal, and a suitable solvent, such as for example ethylacetate.

Compounds of formula (I) wherein R^3 comprises C_{2-6}alkynyl, can be hydrogenated into a compound of formula (I) wherein R^3 comprises C_{2-6}alkenyl in the presence of a suitable catalyst, such as for example Lindlar catalyst, and a suitable solvent, such as for example ethylacetate.

Compounds of formula (I) wherein R^3 represents C_{1-6}alkyl substituted with —P(═O)(OC_{1-6}alkyl)$_2$ can be converted into a compound of formula (I) wherein R^3 represents C_{1-6}alkyl substituted with —P(═O)(OH)$_2$ by reaction with bromotrimethylsilane in the presence of a suitable solvent, such as for example dichloromethane.

Compounds of formula (I) wherein the R^9 substituent is substituted with ═O, can be converted into the corresponding reduced R^9 substituent by reaction with a suitable reducing agent, such as for example $LiAlH_4$ in a suitable solvent, such as for example tetrahydrofuran.

Compounds of formula (I) wherein R^3 comprises —NHR^{10} can be converted into a compound of formula (I) wherein R^3 comprises —NR^{10}—(C═O)-optionally substituted C_{1-6}alkyl, by reaction with the corresponding W—(C═O)-optionally substituted C_{1-6}alkyl wherein W represents a suitable leaving group, such as for example halo, e.g. chloro and the like, in the presence of a suitable base, such as for example triethylamine, and a suitable solvent, such as for example acetonitrile.

Compounds of formula (I) wherein R^3 represents C_{1-6}alkyl substituted with NR^{10}(benzyl) can be converted into a compound of formula (I) wherein R^3 represents C_{1-6}alkyl substituted with NHR^{10}, by reaction with 1-chloroethylchloroformate in the presence of a suitable solvent, such as for example dichloromethane

Compounds of formula (I) wherein R^1 represents unsubstituted piperidine, can be converted into a compound of formula (I) wherein R^1 represents 1-methyl-piperidine, by reaction with iodomethane in the presence of a suitable base, such as for example potassium carbonate, and a suitable solvent, such as for example acetonitrile.

Compounds of formula (I) wherein R^1 represents hydrogen can be converted into a compound of formula (I) wherein R^1 represents optionally substituted C_{1-6}alkyl, by reaction with optionally substituted C_{1-6}alkyl-W wherein W represents a suitable leaving group, such as for example halo, e.g. bromo and the like, in the presence of a suitable base, such as for example potassium carbonate, and a suitable solvent, such as for example acetonitrile.

Compounds of formula (I) wherein R^2 represents halo, e.g. bromo, can be converted into a compound of formula (I) wherein R^2 represents cyano, by reaction with zinc cyanide, in the presence of a suitable catalyst, such as for example $Pd_2(dba)_3$ and a suitable ligand, such as for example 1,1-bis(diphenylphosphino)ferrocene, in the presence of a suitable solvent, such as for example N,N-dimethylformamide.

Said R^2 substituent being cyano can be converted into CH_2—NH_2 by hydrogenation in the presence of NH_3 and Nickel.

Compounds of formula (I) wherein R^2 represents OCH_3 can be converted into a compounds of formula (I) wherein R^2 represents OH by reaction with boron tribromide in the presence of a suitable solvent, such as for example dichloromethane.

Compounds of formula (I) wherein R^2 represents OH can be converted into a compounds of formula (I) wherein R^2 represents OCH_3 by reaction with methyl iodine in the presence of a suitable base, such as for example potassium carbonate, and a suitable solvent, such as for example N,N-dimethylformamide.

Compounds of formula (I) wherein R^2 represents hydrogen, can be converted into a compound of formula (I) wherein R^2 represents —CHOH—CF_3 by reaction with trifluoroacetaldehyde methyl hemiketal.

Compounds of formula (I) wherein R^{3a} and R^{3b} are taken together to form ═O can be converted into a compound of formula (I) wherein R^{3a} is hydroxyl and R^{3b} is hydrogen in the presence of a suitable reducing agent, such as for example sodium borohydride, and a suitable solvent, such as for example an alcohol, e.g. methanol.

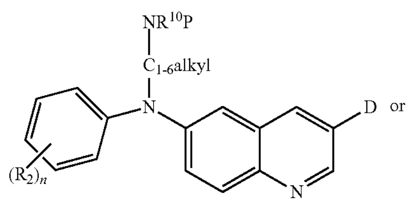
Compounds of formula (I) wherein R^{3a} and R^{3b} are taken together to form =O can also be converted into a compound of formula (I) wherein R^{3a} and R^{3b} are taken together to form =—CN in the presence of diethyl cyanomethylphosphonate, a suitable base, such as for example sodium hydride, and a suitable solvent, such as for example tetrahydrofuran. The resulting compounds can be converted into a compound of formula (I) wherein R^{3a} is CH_2—CN or —CH_2—C(=O)—NH_2 and R^{3b} is hydrogen, in the presence of sodium borohydride in pyridine/methanol.

For the conversion reactions, reference is also made to the examples described in the Experimental Part hereinafter.

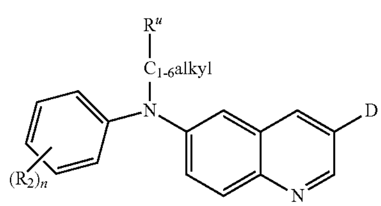
A further aspect of the invention is a process for the preparation of a compound of formula (I) as defined herein, which process comprises:

(i) deprotecting a compound of formula (XXX) wherein P represents a suitable protective group, such as for example a butyloxycarbonyl-group (—$CO_2C(CH_3)_3$) in the presence of a suitable acid, such as for example HCl or trifluoroacetic acid;

(XXX)



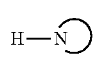
(ii) the reaction of a compound of the formula (IX) or (IX'):



(IX): R^u is —O—(S=O)$_2$—CH_3
(IX'): R^u is Cl

or a protected form thereof, with an appropriately substituted amine or a reactive

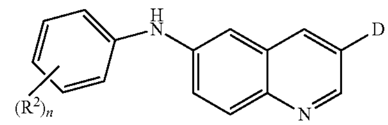
derivative thereof, such as for example $NHR^{10}R^{11}$ (X), $NHR^{10}P$ (X-a) or



(XXI), for example in a sealed vessel, in the presence of a suitable base, such as for example sodium hydride and/or in the presence or absence of a solvent such as acetonitrile, N,N-dimethylformamide or N,N-dimethylacetamide; or

(iii) the reaction of a compound of the formula (VI):

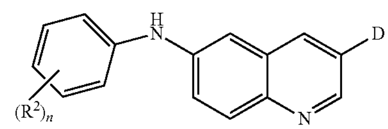
(VI)



or a protected form thereof, with a compound of formula W_6—C_{1-6}alkyl-$NR^{10}P$ wherein P represents a suitable protective group and W_6 represents a suitable leaving group, such as for example halo, e.g. bromo and the like, or —O—S(=O)$_2$—CH_3, in the presence of a suitable base, such as for example sodium hydride, and a suitable solvent, e.g. N,N-dimethylformamide or N,N-dimethylacetamide, followed by removing P and optionally removing any further protecting group present; or

(iv) the reaction of a compound of the formula (VI):

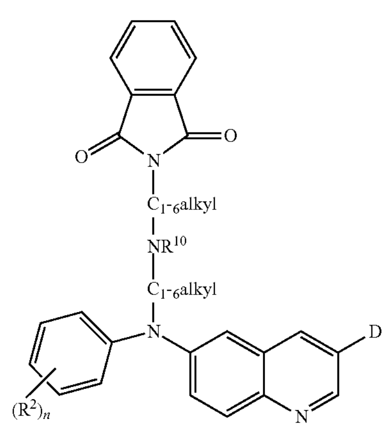
(VI)



or a protected thereof, with a compound of formula W_6—C_{1-6}alkyl-NHR^{10} wherein W_6 represents a suitable leaving group, such as for example halo, e.g. bromo and the like, or —O—S(=O)$_2$—CH_3, in the presence of a suitable base, such as for example sodium hydride, and a suitable solvent, e.g. N,N-dimethylformamide or N,N-dimethylacetamide; or this type of reaction can also be performed in the presence of a suitable phase transfer agent, such as for example tetrabutylammonium bromide, a suitable base, such as for example potassium hydroxide, and a suitable solvent, such as for example 2-methyl-tetrahydrofuran and water;

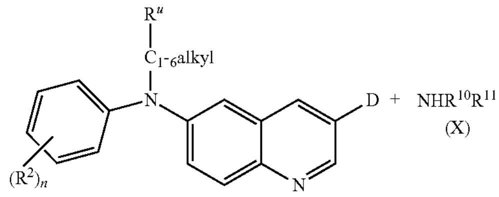
(v) the reaction of a compound of formula (XXXVI)

(XXXVI)



with hydrazine in the presence of a suitable solvent, such as for example an alcohol, e.g. ethanol;

(vi) the reaction of a compound of formula (IX-1) wherein R^u represents O—S(=O)$_2$—CH_3,

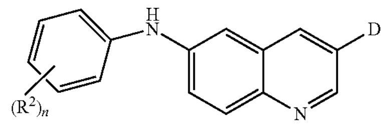

(X)

(IX-1)

with an intermediate of formula (X) in the presence of a suitable solvent, such as for example acetonitrile;

(vii) the reaction of a compound of formula (VI)

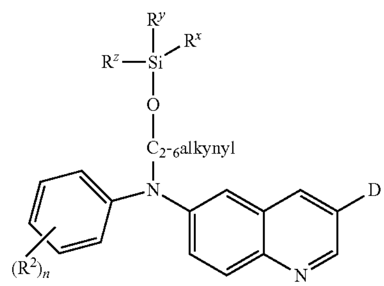
(VI)



with an intermediate of formula W_{11}—R^{3b} wherein R^{3b} represents optionally substituted C_{2-6}alkynyl and W_{11} represents a suitable leaving group such as for example halo, e.g. chloro, or —O—S(=O)$_2$—CH_3, in the presence of a suitable base, such as for example NaH, and a suitable solvent, such as for example N,N-dimethylformamide;

(viii) the reaction of a compound of formula (VIII') wherein R^x and R^y represent C_{1-4}alkyl, and R^z represent C_{1-4}alkyl or phenyl,

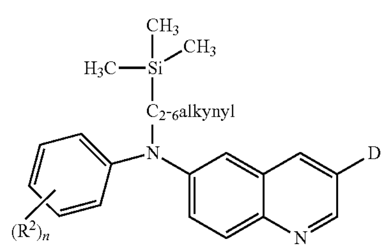
(VIII')



with a suitable acid, such as for example trifluoroacetic acid, in the presence of a suitable solvent, such as for example tetrahydrofuran;

(viii) deprotecting a compound of formula (XXXXII)

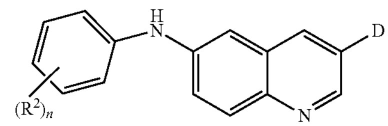
(XXXXII)



in the presence of a suitable base, such as for example K_2CO_3, and a suitable solvent, such as for example an alcohol, e.g. methanol and the like;

(ix) the reaction of a compound of formula (VI)

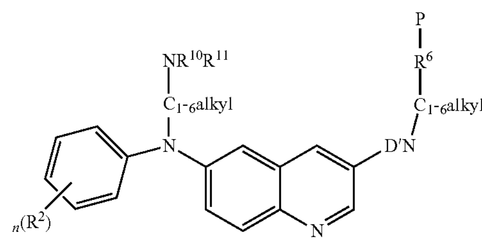
(VI)



with di(C_{1-6}alkyl)vinylphosphonate in the presence of a suitable catalyst, such as for example tri-N-butylphosphine, and a suitable solvent, such as for example acetonitrile;

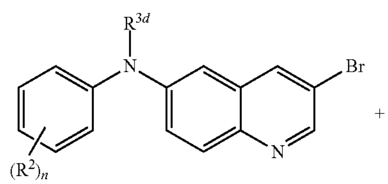
(x) deprotecting a compound of formula (XXXXI) wherein the D'N moiety represents a D moiety wherein the D moiety contains a nitrogen atom

(XXXXI)

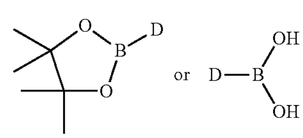


in the presence of a suitable base, such as for example K_2CO_3, and a suitable solvent, such as for example an alcohol, e.g. methanol and the like;

(xi) the reaction of a compound of formula (XIX) with a compound of formula (III) or (III-a)



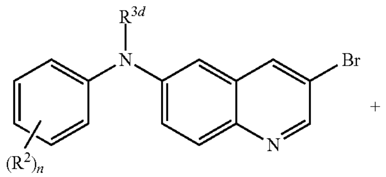
(XIX)



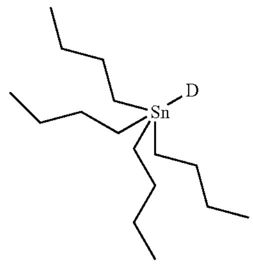
(III) (III-a)

in the presence of a suitable catalyst, such as for example tetrakis(triphenyl)phosphine palladium or $Pd_2(dba)_3$ (tris (dibenzylideneacetone) dipalladium (0)), a suitable ligand, such as 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl, a suitable base, such as for example Na_2CO_3 or K_3PO_4, and a suitable solvent, such as for example ethylene glycol dimethylether or dioxane or water;

(xi-1) the reaction of a compound of formula (XIX) with a compound of formula (XXXVII)



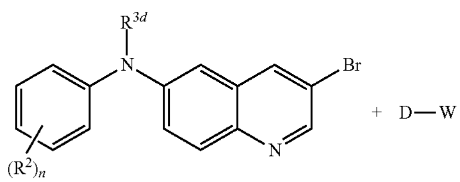
(XIX)



(XXXVII)

in the presence of a suitable catalyst, such as for example tetrakis(triphenyl)phosphine palladium, and a suitable solvent, such as for example N,N-dimethylformamide or toluene.

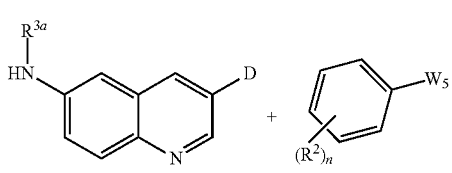
(xi-2) the reaction of a compound of formula (XIX) with D-W, wherein W represents a suitable leaving group, such as for example halo, e.g. bromo, iodo and the like,



(XIX)

in the presence of a suitable catalyst, such as for example tetrakis(triphenyl)phosphine palladium, ethylmagnesium chloride, zinc chloride to generated in situ a reactive organometallic species, and a suitable solvent, such as for example tetrahydrofuran.

(xii) the reaction of a compound of formula (XX) wherein R^{3a} represents optionally substituted C_{1-6}alkyl, with a compound of formula (XIV)

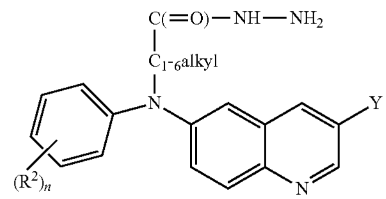


(XX) (XIV)

in the presence of a suitable catalyst, such as for example palladium (II) acetate or $Pd_2(dba)_3$ (tris(dibenzylidene acetone) dipalladium (0)), a suitable ligand such as for example 2-dicyclohexylphosphino-tris-isopropyl-biphenyl or 1,1'-[1,1'-binaphthalene]-2,2'-diylbis[1,1-diphenylphosphine], a suitable base, such as for example sodium tert-butoxide, and a suitable solvent, such as for example ethylene glycol dimethylether;

(xiii) the reaction of a compound of formula (XXXI)

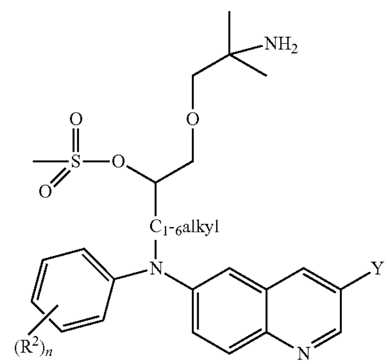
(XXXI)



with W_8—CN, wherein W_8 represents a suitable leaving group, such as for example halo, e.g. bromo, in the presence of a suitable base, such as for example $NaHCO_3$, and a suitable solvent, such as for example water or dioxane;

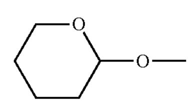
(xiv) the reaction of a compound of formula (XXXV)

(XXXV)



with a suitable base, such as for example N,N-diisopropylethylamine and triethylamine, in the presence of a suitable solvent, such as for example an alcohol, e.g. methanol;

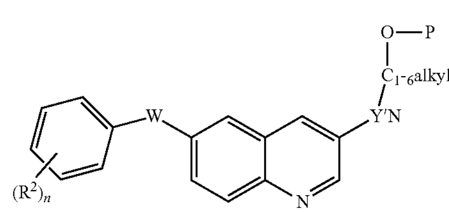
(xv) deprotecting a compound of formula (XXVI) wherein P represents a suitable protective group such as for example O—$Si(CH_3)_2(C(CH_3)_3)$ or



,

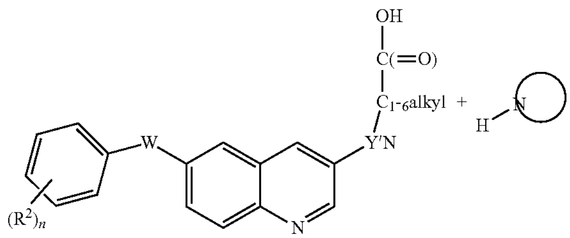
and wherein Y'N represents an -E-D moiety wherein the D ring moiety contains a nitrogen atom

(XXVI)



in the presence of a suitable acid, such as for example HCl or trifluoroacetic acid, or a suitable de-silylating agent, such as for example tetrabutyl ammonium fluoride, and a suitable solvent, such as an alcohol, e.g. methanol, or tetrahydrofuran;

(xvi) the reaction of a compound of formula (XXIX) wherein Y'N represents an -E-D moiety wherein the D ring moiety contains a nitrogen atom, with a compound of formula (XXI)

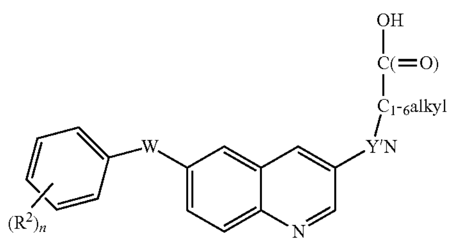


(XXIX) (XXI)

in the presence of suitable peptide coupling reagents such as, 1-hydroxy-benzotriazole and 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide HCl;

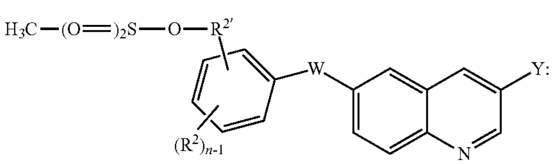
(xvii) the reaction of a compound of formula (XXIX) wherein Y'N represents an -E-D moiety wherein the D ring moiety contains a nitrogen atom

(XXIX)



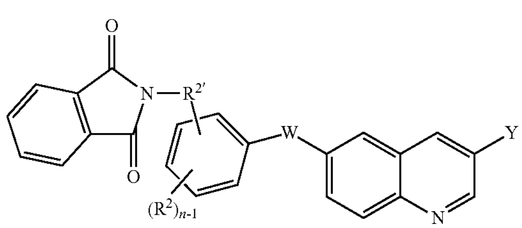
with NHR^4R^5 in the presence of suitable peptide coupling reagents such as 1-hydroxy-benzotriazole and 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide HCl and a suitable base, such as triethylamine, and a suitable solvent, such as for example dichloromethane;

(xviii) reacting the below compound



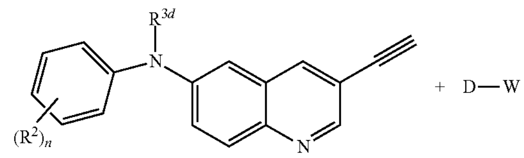
with NHR^7R^8 in the presence of a suitable base, such as for example K_2CO_3, and a suitable solvent, such as for example tetrahydrofuran;

(xviii) deprotecting the below compound



in the presence of hydrazine monohydrate, and a suitable solvent, such as for example an alcohol, e.g. ethanol;

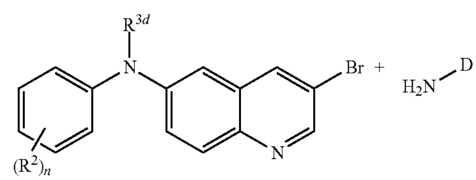
(xix) the reaction of a compound of formula (XLI) with D-W



(XLI)

in the presence of a suitable catalyst, such as for example dichlorobis(triphenylphosphine) palladium (II) and copperiodide, a suitable base, such as for example triethylamine, and a suitable solvent, such as for example N,N-dimethylformamide and acetonitrile;

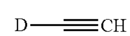
(xx) the reaction of a compound of formula (XIX) with $D\text{-}NH_2$

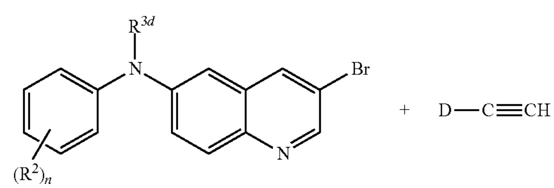


(XIX)

in the presence of a suitable catalyst, such as for example (tris(dibenzylideneacetone) dipalladium (0)), a suitable ligand, such as for example 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene, a suitable base, such as for example cesium carbonate, and a suitable solvent, such as for example dioxane;

(xxi) the reaction of a compound of formula (XIX) with

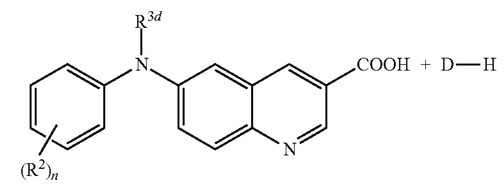




(XIX)

in the presence of a suitable catalyst, such as for example dichlorobis(triphenylphosphine) palladium (II) and copperiodide, a suitable ligand, such as for example triphenylphosphine, a suitable base, such as for example triethylamine, and a suitable solvent, such as for example N,N-dimethylformamide

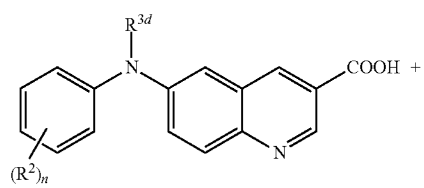
(xxii) the reaction of a compound of formula (XLII) with D-H



(XLII)

in the presence of suitable peptide coupling reagents such as for example 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and 1-hydroxybenzotriazole, a suitable base, such as for example triethylamine, and a suitable solvent, such as for example methylene chloride

(xxiii) the reaction of a compound of formula (XLII) with D-$(CR^xR^y)_s$—NH_2

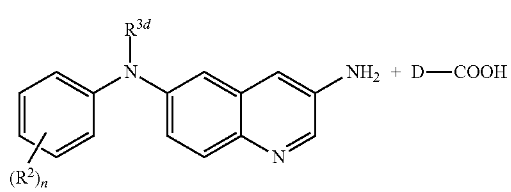


(XLII)

D—$(CR^xR^y)_s$—NH_2

in the presence of suitable peptide coupling reagents such as for example 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and 1-hydroxybenzotriazole, a suitable base, such as for example triethylamine, and a suitable solvent, such as for example methylene chloride,

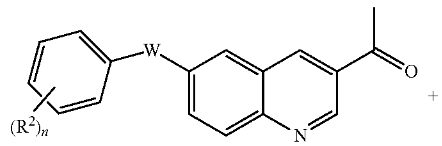
(xxiv) the reaction of a compound of formula (XLIII) with D-COOH



(XLIII)

in the presence of suitable peptide coupling reagents such as for example 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and 1-hydroxybenzotriazole, a suitable base, such as for example triethylamine, and a suitable solvent, such as for example methylene chloride

(xxv) the reaction of a compound of formula (XLVI) with R^{19}—O—NH_2

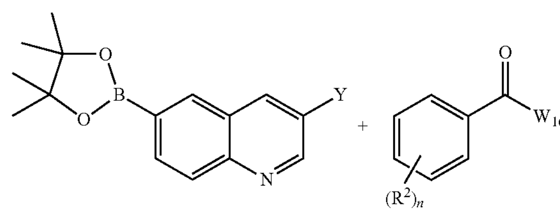


(XLVI)

R^{19}—O—NH_2

in the presence of a suitable base such as for example pyridine, and a suitable solvent, such as for example an alcohol, e.g. ethanol,

(xxvi) the reaction of a compound of formula (XLX) with a compound of formula (XLIX) wherein W_{16} represents a suitable leaving group such as for example halo, e.g. bromo and the like,

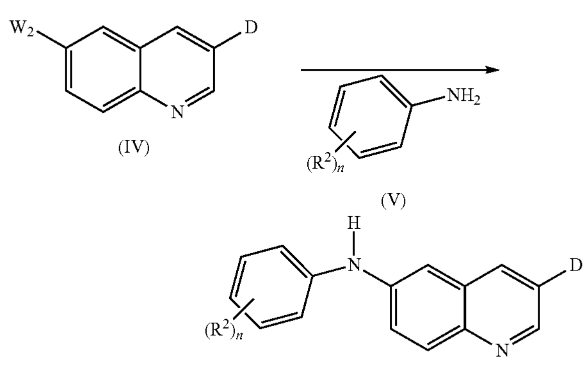


(XLX) (XLIX)

in the presence of a catalyst, such as for example dichlorobis (triphenylphosphine)palladium, a suitable base, such as for example Na_2CO_3, and a suitable solvent, such as for example tetrahydrofuran

wherein the variables are as defined herein; and optionally thereafter converting one compound of the formula (I) into another compound of the formula (I).

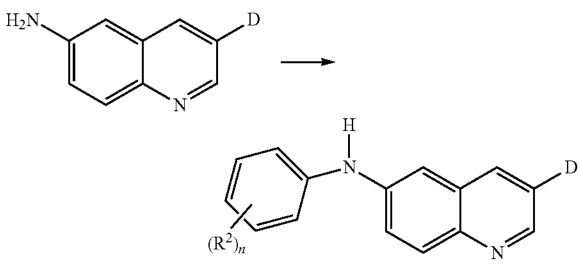
A further embodiment is a process for synthesis of a compound of formula (VI) wherein:



(IV) (V) (VI)

a compound of formula (IV) is reacted with an intermediate of formula (V) in the presence of a suitable catalyst, such as for example palladium (II) acetate, a suitable base, such as sodium tert-butoxide or Cs_2CO_3, a suitable ligand, such as for example 1,1'-[1,1'-binaphthalene]-2,2'-diylbis[1,1-diphenylphosphine], and a suitable solvent or solvent mixture, such as for example dioxane or ethylene glycol dimethylether and water.

A further embodiment is a process for synthesis of a compound of formula (VI) wherein:

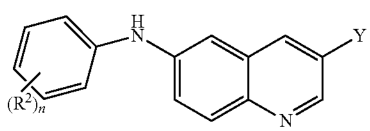


(VI)

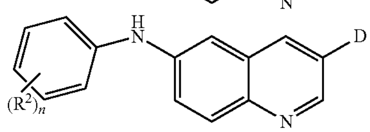
the 6-aminoquinoline derivative is reacted with a halophenyl derivative, such as a bromo or iodo phenyl derivative, in the presence of a suitable catalyst, such as for example tris (dibenzylideneacetone) dipalladium(0), a suitable base, such as Cs_2CO_3, a suitable ligand, such as for example 2-dicyclohexylphosphino-2',4',6'-tri-i-propyl-1,1'-biphenyl or xantphos in a suitable solvent or solvent mixture, such as for example 2-methyl-2-propanol to result in an intermediate of formula (VI).

In a further embodiment the invention provides a novel intermediate. In one embodiment the invention provides any of the novel intermediates described above. In another embodiment the invention provides a novel intermediate of formula (VI) or formula (IX).

In one embodiment, the present invention also relates to a compound having the

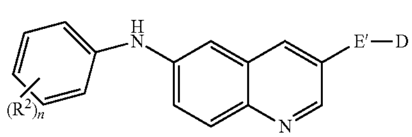


or



or

following formula:



wherein E' represents —$(CR^{22}R^{23})_n$—, C_{2-4}alkenediyl optionally substituted with R^{22}, C_{2-4}alkynediyl optionally substituted with R^{22}, —CO—$(CR^{22}R^{23})_s$—, —$(CR^{22}R^{23})_s$—O—, —NR^{22}—$(CR^{22}R^{23})_s$—, —$(CR^{22}R^{23})_s$—NR^{22}—, —O—$(CR^{22}R^{23})_s$—, —$(CR^{22}R^{23})_s$—O—, —$S(O)_m$—$(CR^{22}R^{23})_s$—, —$(CR^{22}R^{23})_s S(O)_m$—, —$(CR^{22}R^{23})_s$—CO—NR^{22}—$(CR^{22}R^{23})_s$— or —$(CR^{22}R^{23})_s$—NR^{22}—CO—$(CR^{22}R^{23})_s$—;

wherein Y, D, R^2, and n are as defined for a compound of formula (I) above.

Pharmaceutically Acceptable Salts, Solvates or Derivatives Thereof.

In this section, as in all other sections of this application, unless the context indicates otherwise, references to formula (I) include references to all other sub-groups, preferences, embodiments and examples thereof as defined herein.

Unless otherwise specified, a reference to a particular compound also includes ionic forms, salts, solvates, isomers, tautomers, N-oxides, esters, prodrugs, isotopes and protected forms thereof, for example, as discussed below; preferably, the ionic forms, or salts or tautomers or isomers or N-oxides or solvates thereof; and more preferably, the ionic forms, or salts or tautomers or solvates or protected forms thereof, even more preferably the salts or tautomers or solvates thereof. Many compounds of the formula (I) can exist in the form of salts, for example acid addition salts or, in certain cases salts of organic and inorganic bases such as carboxylate, sulphonate and phosphate salts. All such salts are within the scope of this invention, and references to compounds of the formula (I) include the salt forms of the compounds. It will be appreciated that references to "derivatives" include references to ionic forms, salts, solvates, isomers, tautomers, N-oxides, esters, prodrugs, isotopes and protected forms thereof.

According to one aspect of the invention there is provided a compound as defined herein or a salt, tautomer, N-oxide or solvate thereof. According to a further aspect of the invention there is provided a compound as defined herein or a salt or solvate thereof. References to compounds of the formula (I) and sub-groups thereof as defined herein include within their scope the salts or solvates or tautomers or N-oxides of the compounds.

The salt forms of the compounds of the invention are typically pharmaceutically acceptable salts, and examples of pharmaceutically acceptable salts are discussed in Berge et al. (1977) "Pharmaceutically Acceptable Salts," *J. Pharm. Sci.*, Vol. 66, pp. 1-19. However, salts that are not pharmaceutically acceptable may also be prepared as intermediate forms which may then be converted into pharmaceutically acceptable salts.

Such non-pharmaceutically acceptable salts forms, which may be useful, for example, in the purification or separation of the compounds of the invention, also form part of the invention.

The salts of the present invention can be synthesized from the parent compound that contains a basic or acidic moiety by conventional chemical methods such as methods described in *Pharmaceutical Salts: Properties, Selection, and Use*, P. Heinrich Stahl (Editor), Camille G. Wermuth (Editor), ISBN: 3-90639-026-8, Hardcover, 388 pages, August 2002. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media such as ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are used. The compounds of the invention may exist as mono- or di-salts depending upon the pKa of the acid from which the salt is formed.

Acid addition salts may be formed with a wide variety of acids, both inorganic and organic. Examples of acid addition salts include salts formed with an acid selected from the group consisting of acetic, 2,2-dichloroacetic, adipic, alginic, ascorbic (e.g. L-ascorbic), L-aspartic, benzenesulphonic, benzoic, 4-acetamidobenzoic, butanoic, (+) camphoric, camphor-sulphonic, (+)-(1S)-camphor-10-sulphonic, capric, caproic, caprylic, cinnamic, citric, cyclamic, dodecylsulphuric, ethane-1,2-disulphonic, ethanesulphonic, 2-hydroxyethanesulphonic, formic, fumaric, galactaric, gentisic, glucoheptonic, D-gluconic, glucuronic (e.g. D-glucuronic), glutamic (e.g. L-glutamic), α-oxoglutaric, glycolic, hippuric, hydrobromic, hydrochloric, hydriodic, isethionic, lactic (e.g. (+)-L-lactic, (±)-DL-lactic), lactobionic, maleic, malic, (−)-L-malic, malonic, (±)-DLmandelic, methanesulphonic, naphthalenesulphonic (e.g. naphthalene-2-sulphonic), naphthalene-1,5-disulphonic, 1-hydroxy-2-naphthoic, nicotinic, nitric, oleic, orotic, oxalic, palmitic, pamoic, phosphoric, propionic, L-pyroglutamic, pyruvic, salicylic, 4-amino-salicylic, sebacic, stearic, succinic, sulphuric, tannic, (+)-L-tartaric, thiocyanic, toluenesulphonic (e.g. p-toluenesulphonic), undecylenic and valeric acids, as well as acylated amino acids and cation exchange resins.

One particular group of salts consists of salts formed from acetic, hydrochloric, hydriodic, phosphoric, nitric, sulphuric, citric, lactic, succinic, maleic, malic, isethionic, fumaric, benzenesulphonic, toluenesulphonic, methanesulphonic (mesylate), ethanesulphonic, naphthalenesulphonic, valeric, acetic, propanoic, butanoic, malonic, glucuronic and lactobionic acids. Another group of acid addition salts includes salts formed from acetic, adipic, ascorbic, aspartic, citric, DL-Lactic, fumaric, gluconic, glucuronic, hippuric, hydrochloric, glutamic, DL-malic, methanesulphonic, sebacic, stearic, succinic and tartaric acids.

If the compound is anionic, or has a functional group which may be anionic (e.g., —COON may be —COO^-), then a salt may be formed with a suitable cation. Examples of suitable inorganic cations include, but are not limited to, alkali metal ions such as Na^+ and K^+, alkaline earth metal cations such as Ca^{2+} and Mg^{2+}, and other cations such as Al^{3+}. Examples of suitable organic cations include, but are not limited to, ammonium ion (i.e., NH_4^+) and substituted ammonium ions (e.g., NH_3R^+, $NH_2R_2^+$, NHR_3^+, NR_4^+).

Examples of some suitable substituted ammonium ions are those derived from: ethylamine, diethylamine, dicyclohexylamine, triethylamine, butylamine, ethylenediamine, ethanolamine, diethanolamine, piperazine, benzylamine, phenylbenzylamine, choline, meglumine, and tromethamine, as well as amino acids, such as lysine and arginine. An example of a common quaternary ammonium ion is $N(CH_3)_4^+$.

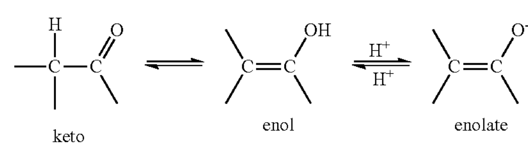
Where the compounds of the formula (I) contain an amine function, these may form quaternary ammonium salts, for example by reaction with an alkylating agent according to methods well known to the skilled person. Such quaternary ammonium compounds are within the scope of formula (I). Compounds of the formula (I) containing an amine function may also form N-oxides. A reference herein to a compound of the formula (I) that contains an amine function also includes the N-oxide. Where a compound contains several amine functions, one or more than one nitrogen atom may be oxidised to form an N-oxide. Particular examples of N-oxides are the N-oxides of a tertiary amine or a nitrogen atom of a nitrogen-containing heterocycle. N-Oxides can be formed by treatment of the corresponding amine with an oxidizing agent such as hydrogen peroxide or a per-acid (e.g. a peroxycarboxylic acid), see for example *Advanced Organic Chemistry*, by Jerry March, 4th Edition, Wiley Interscience, pages. More particularly, N-oxides can be made by the procedure of L. W. Deady (*Syn. Comm.* (1977), 7, 509-514) in which the amine compound is reacted with m-chloroperoxybenzoic acid (MCPBA), for example, in an inert solvent such as dichloromethane.

The compounds of the invention may form solvates, for example with water (i.e., hydrates) or common organic solvents. As used herein, the term "solvate" means a physical association of the compounds of the present invention with one or more solvent molecules. This physical association involves varying degrees of ionic and covalent bonding, including hydrogen bonding. In certain instances the solvate will be capable of isolation, for example when one or more solvent molecules are incorporated in the crystal lattice of the crystalline solid. The term "solvate" is intended to encompass both solution-phase and isolatable solvates. Non-limiting examples of suitable solvates include compounds of the invention in combination with water, isopropanol, ethanol, methanol, DMSO, ethyl acetate, acetic acid or ethanolamine and the like. The compounds of the invention may exert their biological effects whilst they are in solution.

Solvates are well known in pharmaceutical chemistry. They can be important to the processes for the preparation of a substance (e.g. in relation to their purification, the storage of the substance (e.g. its stability) and the ease of handling of the substance and are often formed as part of the isolation or purification stages of a chemical synthesis. A person skilled in the art can determine by means of standard and long used techniques whether a hydrate or other solvate has formed by the isolation conditions or purification conditions used to prepare a given compound. Examples of such techniques include thermogravimetric analysis (TGA), differential scanning calorimetry (DSC), X-ray crystallography (e.g. single crystal X-ray crystallography or X-ray powder diffraction) and Solid State NMR (SS-NMR, also known as Magic Angle Spinning NMR or MAS-NMR). Such techniques are as much a part of the standard analytical toolkit of the skilled chemist as NMR, IR, HPLC and MS. Alternatively the skilled person can deliberately form a solvate using crystallisation conditions that include an amount of the solvent required for the particular solvate. Thereafter the standard methods described above, can be used to establish whether solvates had formed. Also encompassed by formula (I) are any complexes (e.g. inclusion complexes or clathrates with compounds such as cyclodextrins, or complexes with metals) of the compounds.

Furthermore, the compounds of the present invention may have one or more polymorph (crystalline) or amorphous forms and as such are intended to be included in the scope of the invention.

Compounds of the formula (I) may exist in a number of different geometric isomeric, and tautomeric forms and references to compounds of the formula (I) include all such forms. For the avoidance of doubt, where a compound can exist in one of several geometric isomeric or tautomeric forms and only one is specifically described or shown, all others are nevertheless embraced by formula (I). Other examples of tautomeric forms include, for example, keto-, enol-, and enolate-forms, as in, for example, the following tautomeric pairs: keto/enol (illustrated below), imine/enamine, amide/imino alcohol, amidine/enediamines, nitroso/oxime, thioketone/enethiol, and nitro/aci-nitro.



Where compounds of the formula (I) contain one or more chiral centres, and can exist in the form of two or more optical isomers, references to compounds of the formula (I) include all optical isomeric forms thereof (e.g. enantiomers, epimers and diastereoisomers), either as individual optical isomers, or mixtures (e.g. racemic mixtures) of two or more optical isomers, unless the context requires otherwise. The optical isomers may be characterised and identified by their optical activity (i.e. as + and isomers, or d and/isomers) or they may be characterised in terms of their absolute stereochemistry using the "R and S" nomenclature developed by Cahn, Ingold and Prelog, see *Advanced Organic Chemistry* by Jerry March, 4th Edition, John Wiley & Sons, New York, 1992, pages 109-114, and see also Cahn, Ingold & Prelog (1966) *Angew. Chem. Int. Ed. Engl.*, 5, 385-415. Optical isomers can be separated by a number of techniques including chiral chromatography (chromatography on a chiral support) and such techniques are well known to the person skilled in the art. As an alternative to chiral chromatography, optical isomers can be separated by forming diastereoisomeric salts with chiral acids such as (+)-tartaric acid, (−)-pyroglutamic acid, (−)-di-toluoyl-L-tartaric acid, (+)-mandelic acid, (−)-malic acid, and (−)-camphorsulphonic, separating the diastereoisomers by preferential crystallisation, and then dissociating the salts to give the individual enantiomer of the free base.

Where compounds of the formula (I) exist as two or more optical isomeric forms, one enantiomer in a pair of enantiomers may exhibit advantages over the other enantiomer, for example, in terms of biological activity. Thus, in certain circumstances, it may be desirable to use as a therapeutic agent only one of a pair of enantiomers, or only one of a plurality of diastereoisomers. Accordingly, the invention provides compositions containing a compound of the formula (I) having one or more chiral centres, wherein at least 55% (e.g. at least 60%, 65%, 70%, 75%, 80%, 85%, 90% or 95%) of the compound of the formula (I) is present as a single optical isomer (e.g. enantiomer or diastereoisomer). In one general embodiment, 99% or more (e.g. substantially all) of the total amount of the compound of the formula (I) may be present as a single optical isomer (e.g. enantiomer or diastereoisomer). When a specific isomeric form is identified (e.g. S configuration, or E isomer), this means that said isomeric form is substantially free of the other isomer(s), i.e. said isomeric form is present in at least 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 99% or more (e.g. substantially all) of the total amount of the compound of the invention.

The compounds of the invention include compounds with one or more isotopic substitutions, and a reference to a particular element includes within its scope all isotopes of the element. For example, a reference to hydrogen includes within its scope ^{1}H, ^{2}H (D), and ^{3}H (T). Similarly, references to carbon and oxygen include within their scope respectively ^{12}C, ^{13}C and ^{14}C and ^{16}O and ^{18}O. The isotopes may be radioactive or non-radioactive. In one embodiment of the invention, the compounds contain no radioactive isotopes. Such compounds are preferred for therapeutic use. In another embodiment, however, the compound may contain one or more radioisotopes. Compounds containing such radioisotopes may be useful in a diagnostic context.

Esters such as carboxylic acid esters and acyloxy esters of the compounds of formula (I) bearing a carboxylic acid group or a hydroxyl group are also embraced by formula (I). In one embodiment of the invention, formula (I) includes within its scope esters of compounds of the formula (I) bearing a carboxylic acid group or a hydroxyl group. In another embodiment of the invention, formula (I) does not include within its scope esters of compounds of the formula (I) bearing a carboxylic acid group or a hydroxyl group. Examples of esters are compounds containing the group —C(═O)OR, wherein R is an ester substituent, for example, a C_{1-6} alkyl group, a heterocyclyl group, or a C_{5-20} aryl group, preferably a C_{1-6} alkyl group. Particular examples of ester groups include, but are not limited to, —C(═O)OCH_3, —C(═O)OCH_2CH_3, —C(═O)OC$(CH_3)_3$, and —C(═O)OPh. Examples of acyloxy (reverse ester) groups are represented by —OC(═O)R, wherein R is an acyloxy substituent, for example, a C_{1-7} alkyl group, a C_{3-20} heterocyclyl group, or a C_{5-20} aryl group, preferably a C_{1-7} alkyl group. Particular examples of acyloxy groups include, but are not limited to, —OC(═O)CH_3 (acetoxy), —OC(═O)CH_2CH_3, —OC(═O)C$(CH_3)_3$, —OC(═O)Ph, and —OC(═O)CH_2Ph.

For example, some prodrugs are esters of the active compound (e.g., a physiologically acceptable metabolically labile ester). By "prodrugs" is meant for example any compound that is converted in vivo into a biologically active compound of the formula (I).

During metabolism, the ester group (—C(═O)OR) is cleaved to yield the active drug. Such esters may be formed by esterification, for example, of any of the carboxylic acid groups (—C(═O)OH) in the parent compound, with, where appropriate, prior protection of any other reactive groups present in the parent compound, followed by deprotection if required.

Examples of such metabolically labile esters include those of the formula —C(═O)OR wherein R is: C_{1-6}alkyl (e.g., -Me, -Et, -nPr, -iPr, -nBu, -sBu, -iBu, -tBu); C_{1-6}aminoalkyl [e.g., aminoethyl; 2-(N,N-diethylamino)ethyl; 2-(4-morpholino)ethyl); and acyloxy-C_{1-7}alkyl [e.g., acyloxymethyl; acyloxyethyl; pivaloyloxymethyl; acetoxymethyl; 1-acetoxyethyl; 1-(1-methoxy-1-methyl)ethyl-carbonyloxyethyl; 1-(benzoyloxy)ethyl; isopropoxy-carbonyloxymethyl; 1-isopropoxy-carbonyloxyethyl; cyclohexyl-carbonyloxymethyl; 1-cyclohexyl-carbonyloxyethyl; cyclohexyloxy-carbonyloxymethyl; 1-cyclohexyloxy-carbonyloxyethyl; (4-tetrahydropyranyloxy)carbonyloxymethyl; 1-(4-tetrahydropyranyloxy)carbonyloxyethyl; (4-tetrahydropyranyl)carbonyloxymethyl; and 1-(4-tetrahydropyranyl)carbonyloxyethyl]. Also, some prodrugs are activated enzymatically to yield the active compound, or a compound which, upon further chemical reaction, yields the active compound (for example, as in antigen-directed enzyme pro-drug therapy (ADEPT), gene-directed enzyme pro-drug therapy (GDEPT) and ligand-directed enzyme pro-drug therapy (LIDEPT) etc.). For example, the prodrug may be a sugar derivative or other glycoside conjugate, or may be an amino acid ester derivative.

Protein Tyrosine Kinases (PTK)

The compounds of the invention described herein inhibit or modulate the activity of certain tyrosine kinases, and thus the compounds will be useful in the treatment or prophylaxis, in particular the treatment, of disease states or conditions mediated by those tyrosine kinases, in particular FGFR.

FGFR

The fibroblast growth factor (FGF) family of protein tyrosine kinase (PTK) receptors regulates a diverse array of physiologic functions including mitogenesis, wound healing, cell differentiation and angiogenesis, and development. Both normal and malignant cell growth as well as proliferation are affected by changes in local concentration of FGFs, extracellular signalling molecules which act as autocrine as well as paracrine factors. Autocrine FGF signalling may be particularly important in the progression of steroid hormone-dependent cancers to a hormone independent state. FGFs and their receptors are expressed at increased levels in several tissues and cell lines and overexpression is believed to contribute to the malignant phenotype. Furthermore, a number of oncogenes are homologues of genes encoding growth factor receptors, and there is a potential for aberrant activation of FGF-dependent signalling in human pancreatic cancer (Knights et al., Pharmacology and Therapeutics 2010 125:1 (105-117); Korc M. et al Current Cancer Drug Targets 2009 9:5 (639-651)).

The two prototypic members are acidic fibroblast growth factor (aFGF or FGF1) and basic fibroblast growth factor (bFGF or FGF2), and to date, at least twenty distinct FGF family members have been identified. The cellular response to FGFs is transmitted via four types of high affinity transmembrane protein tyrosine-kinase fibroblast growth factor receptors (FGFR) numbered 1 to 4 (FGFR1 to FGFR4).

Disruption of the FGFR1 pathway should affect tumor cell proliferation since this kinase is activated in many tumor types in addition to proliferating endothelial cells. The over-expression and activation of FGFR1 in tumor-associated vasculature has suggested a role for these molecules in tumor angiogenesis.

A recent study has shown a link between FGFR1 expression and tumorigenicity in Classic Lobular Carcinomas (CLC). CLCs account for 10-15% of all breast cancers and, in general, lack p53 and Her2 expression whilst retaining expression of the oestrogen receptor. A gene amplification of 8p12-p11.2 was demonstrated in ~50% of CLC cases and this was shown to be linked with an increased expression of FGFR1. Preliminary studies with siRNA directed against FGFR1, or a small molecule inhibitor of the receptor, showed cell lines harbouring this amplification to be particularly sensitive to inhibition of this signalling pathway. Rhabdomyosarcoma (RMS) is the most common pediatric soft tissue sarcoma likely results from abnormal proliferation and differentiation during skeletal myogenesis. FGFR1 is over-expressed in primary rhabdomyosarcoma tumors and is associated with hypomethylation of a 5' CpG island and abnormal expression of the AKT1, NOG, and BMP4 genes. FGFR1 has also been linked to squamous lung cancer, colorectal cancer, glioblastoma, astrocytomas, prostate cancer, small cell lung cancer, melanoma, head and neck cancer, thyroid cancer, uterine cancer.

Fibroblast growth factor receptor 2 has high affinity for the acidic and/or basic fibroblast growth factors, as well as the keratinocyte growth factor ligands. Fibroblast growth factor receptor 2 also propagates the potent osteogenic effects of FGFs during osteoblast growth and differentiation. Mutations in fibroblast growth factor receptor 2, leading to complex functional alterations, were shown to induce abnormal ossification of cranial sutures (craniosynostosis), implying a major role of FGFR signalling in intramembranous bone formation. For example, in Apert (AP) syndrome, characterized by premature cranial suture ossification, most cases are associated with point mutations engendering gain-of-function in fibroblast growth factor receptor 2. In addition, mutation screening in patients with syndromic craniosynostoses indicates that a number of recurrent FGFR2 mutations accounts for severe forms of Pfeiffer syndrome. Particular mutations of FGFR2 include W290C, D321A, Y340C, C342R, C342S, C342W, N549H, K641R in FGFR2.

Several severe abnormalities in human skeletal development, including Apert, Crouzon, Jackson-Weiss, Beare-Stevenson cutis gyrata, and Pfeiffer syndromes are associated with the occurrence of mutations in fibroblast growth factor receptor 2. Most, if not all, cases of Pfeiffer Syndrome (PS) are also caused by de novo mutation of the fibroblast growth factor receptor 2 gene, and it was recently shown that mutations in fibroblast growth factor receptor 2 break one of the cardinal rules governing ligand specificity. Namely, two mutant splice forms of fibroblast growth factor receptor, FGFR2c and FGFR2b, have acquired the ability to bind to and be activated by atypical FGF ligands.

This loss of ligand specificity leads to aberrant signalling and suggests that the severe phenotypes of these disease syndromes result from ectopic ligand-dependent activation of fibroblast growth factor receptor 2.

Genetic aberrations of the FGFR3 receptor tyrosine kinase such as chromosomal translocations or point mutations result in ectopically expressed or deregulated, constitutively active, FGFR3 receptors. Such abnormalities are linked to a subset of multiple myelomas and in bladder, hepatocellular, oral squamous cell carcinoma and cervical carcinomas. Accordingly, FGFR3 inhibitors would be useful in the treatment of multiple myeloma, bladder and cervical carcinomas. FGFR3 is also over-expressed in bladder cancer, in particular invasive bladder cancer. FGFR3 is frequently activated by mutation in urothelial carcinoma (UC). Increased expression was associated with mutation (85% of mutant tumors showed high-level expression) but also 42% of tumors with no detectable mutation showed over-expression, including many muscle-invasive tumors. FGFR3 is also linked to endometrial and thyroid cancer.

Over expression of FGFR4 has been linked to poor prognosis in both prostate and thyroid carcinomas. In addition a germline polymorphism (Gly388Arg) is associated with increased incidence of lung, breast, colon, liver (HCC) and prostate cancers. In addition, a truncated form of FGFR4 (including the kinase domain) has also been found to be present in 40% of pituitary tumours but not present in normal tissue. FGFR4 overexpression has been observed in liver, colon and lung tumours. FGFR4 has been implicated in colorectal and liver cancer where expression of its ligand FGF19 is frequently elevated. FGFR4 is also linked to astrocytomas, rhabdomyosarcoma.

Fibrotic conditions are a major medical problem resulting from abnormal or excessive deposition of fibrous tissue. This occurs in many diseases, including liver cirrhosis, glomerulonephritis, pulmonary fibrosis, systemic fibrosis, rheumatoid arthritis, as well as the natural process of wound healing. The mechanisms of pathological fibrosis are not fully understood but are thought to result from the actions of various cytokines (including tumor necrosis factor (TNF), fibroblast growth factors (FGF's), platelet derived growth factor (PDGF) and transforming growth factor beta. (TGFβ) involved in the proliferation of fibroblasts and the deposition of extracellular matrix proteins (including collagen and fibronectin). This results in alteration of tissue structure and function and subsequent pathology.

A number of preclinical studies have demonstrated the up-regulation of fibroblast growth factors in preclinical models of lung fibrosis. TGFβ1 and PDGF have been reported to be involved in the fibrogenic process and further published work suggests the elevation of FGF's and consequent increase in fibroblast proliferation, may be in response to elevated TGFβ1. The potential therapeutic benefit of targeting the fibrotic mechanism in conditions such as idiopathic pulmonary fibrosis (IPF) is suggested by the reported clinical effect of the anti-fibrotic agent pirfenidone. Idiopathic pulmonary fibrosis (also referred to as Cryptogenic fibrosing alveolitis) is a progressive condition involving scarring of the lung. Gradually, the air sacs of the lungs become replaced by fibrotic tissue, which becomes thicker, causing an irreversible loss of the tissue's ability to transfer oxygen into the bloodstream. The symptoms of the condition include shortness of breath, chronic dry coughing, fatigue, chest pain and loss of appetite resulting in rapid weight loss. The condition is extremely serious with approximately 50% mortality after 5 years.

As such, the compounds which inhibit FGFR will be useful in providing a means of preventing the growth or inducing apoptosis in tumours, particularly by inhibiting angiogenesis. It is therefore anticipated that the compounds will prove useful in treating or preventing proliferative disorders such as cancers. In particular tumours with activating mutants of receptor tyrosine kinases or upregulation of receptor tyrosine kinases may be particularly sensitive to the inhibitors. Patients with activating mutants of any of the isoforms of the specific RTKs discussed herein may also find treatment with RTK inhibitors particularly beneficial.

Vascular Endothelial Growth Factor (VEGFR)

Chronic proliferative diseases are often accompanied by profound angiogenesis, which can contribute to or maintain an inflammatory and/or proliferative state, or which leads to tissue destruction through the invasive proliferation of blood vessels.

Angiogenesis is generally used to describe the development of new or replacement blood vessels, or neovascularisation. It is a necessary and physiological normal process by which vasculature is established in the embryo. Angiogenesis does not occur, in general, in most normal adult tissues, exceptions being sites of ovulation, menses and wound healing. Many diseases, however, are characterized by persistent and unregulated angiogenesis. For instance, in arthritis, new capillary blood vessels invade the joint and destroy cartilage. In diabetes (and in many different eye diseases), new vessels invade the macula or retina or other ocular structures, and may cause blindness. The process of atherosclerosis has been linked to angiogenesis. Tumor growth and metastasis have been found to be angiogenesis-dependent.

The recognition of the involvement of angiogenesis in major diseases has been accompanied by research to identify and develop inhibitors of angiogenesis. These inhibitors are generally classified in response to discrete targets in the angiogenesis cascade, such as activation of endothelial cells by an angiogenic signal; synthesis and release of degradative enzymes; endothelial cell migration; proliferation of endothelial cells; and formation of capillary tubules. Therefore, angiogenesis occurs in many stages and attempts are underway to discover and develop compounds that work to block angiogenesis at these various stages.

There are publications that teach that inhibitors of angiogenesis, working by diverse mechanisms, are beneficial in diseases such as cancer and metastasis, ocular diseases, arthritis and hemangioma.

Vascular endothelial growth factor (VEGF), a polypeptide, is mitogenic for endothelial cells in vitro and stimulates angiogenic responses in vivo. VEGF has also been linked to inappropriate angiogenesis. VEGFR(s) are protein tyrosine kinases (PTKs). PTKs catalyze the phosphorylation of specific tyrosine residues in proteins involved in cell function thus regulating cell growth, survival and differentiation.

Three PTK receptors for VEGF have been identified: VEGFR-1 (Flt-1); VEGFR-2 (Flk-1 or KDR) and VEGFR-3 (Flt-4). These receptors are involved in angiogenesis and participate in signal transduction. Of particular interest is VEGFR-2, which is a transmembrane receptor PTK expressed primarily in endothelial cells. Activation of VEGFR-2 by VEGF is a critical step in the signal transduction pathway that initiates tumour angiogenesis. VEGF expression may be constitutive to tumour cells and can also be upregulated in response to certain stimuli. One such stimuli is hypoxia, where VEGF expression is upregulated in both tumour and associated host tissues. The VEGF ligand activates VEGFR-2 by binding with its extracellular VEGF binding site. This leads to receptor dimerization of VEGFRs and autophosphorylation of tyrosine residues at the intracellular kinase domain of VEGFR-2. The kinase domain operates to transfer a phosphate from ATP to the tyrosine residues, thus providing binding sites for signalling proteins downstream of VEGFR-2 leading ultimately to initiation of angiogenesis.

Inhibition at the kinase domain binding site of VEGFR-2 would block phosphorylation of tyrosine residues and serve to disrupt initiation of angiogenesis.

Angiogenesis is a physiologic process of new blood vessel formation mediated by various cytokines called angiogenic factors. Although its potential pathophysiologic role in solid tumors has been extensively studied for more than 3 decades, enhancement of angiogenesis in chronic lymphocytic leukemia (CLL) and other malignant hematological disorders has been recognized more recently. An increased level of angiogenesis has been documented by various experimental methods both in bone marrow and lymph nodes of patients with CLL. Although the role of angiogenesis in the pathophysiology of this disease remains to be fully elucidated, experimental data suggest that several angiogenic factors play a role in the disease progression. Biologic markers of angiogenesis were also shown to be of prognostic relevance in CLL. This indicates that VEGFR inhibitors may also be of benefit for patients with leukemia's such as CLL.

In order for a tumour mass to get beyond a critical size, it must develop an associated vasculature. It has been proposed that targeting a tumor vasculature would limit tumor expansion and could be a useful cancer therapy. Observations of tumor growth have indicated that small tumour masses can persist in a tissue without any tumour-specific vasculature. The growth arrest of nonvascularized tumors has been attributed to the effects of hypoxia at the center of the tumor. More recently, a variety of proangiogenic and antiangiogenic factors have been identified and have led to the concept of the "angiogenic switch," a process in which disruption of the normal ratio of angiogenic stimuli and inhibitors in a tumor mass allows for autonomous vascularization. The angiogenic switch appears to be governed by the same genetic alterations that drive malignant conversion: the activation of oncogenes and the loss of tumour suppressor genes. Several growth factors act as positive regulators of angiogenesis. Foremost among these are vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), and angiogenin. Proteins such as thrombospondin (Tsp-1), angiostatin, and endostatin function as negative regulators of angiogenesis.

Inhibition of VEGFR2 but not VEGFR1 markedly disrupts angiogenic switching, persistent angiogenesis, and initial tumor growth in a mouse model. In late-stage tumors, phenotypic resistance to VEGFR2 blockade emerged, as tumors regrew during treatment after an initial period of growth suppression. This resistance to VEGF blockade involves reactivation of tumour angiogenesis, independent of VEGF and associated with hypoxia-mediated induction of other proangiogenic factors, including members of the FGF family. These other proangiogenic signals are functionally implicated in the revascularization and regrowth of tumours in the evasion phase, as FGF blockade impairs progression in the face of VEGF inhibition.

There is evidence for normalization of glioblastoma blood vessels in patients treated with a pan-VEGF receptor tyrosine kinase inhibitor, AZD2171, in a phase 2 study. MRI determination of vessel normalization in combination with circulating biomarkers provides for an effective means to assess response to antiangiogenic agents.

PDGFR

A malignant tumour is the product of uncontrolled cell proliferation. Cell growth is controlled by a delicate balance between growth-promoting and growth-inhibiting factors. In normal tissue the production and activity of these factors results in differentiated cells growing in a controlled and regulated manner that maintains the normal integrity and functioning of the organ. The malignant cell has evaded this control; the natural balance is disturbed (via a variety of mechanisms) and unregulated, aberrant cell growth occurs. A growth factor of importance in tumour development is the platelet-derived growth factor (PDGF) that comprises a family of peptide growth factors that signal through cell surface tyrosine kinase receptors (PDGFR) and stimulate various cellular functions including growth, proliferation, and differentiation.

Advantages of a Selective Inhibitor

Development of FGFR kinase inhibitors with a differentiated selectivity profile provides a new opportunity to use these targeted agents in patient sub-groups whose disease is driven by FGFR deregulation. Compounds that exhibit reduced inhibitory action on additional kinases, particularly VEGFR2 and PDGFR-beta, offer the opportunity to have a differentiated side-effect or toxicity profile and as such allow for a more effective treatment of these indications. Inhibitors of VEGFR2 and PDGFR-beta are associated with toxicities such as hypertension or oedema respectively. In the case of VEGFR2 inhibitors this hypertensive effect is often dose limiting, may be contraindicated in certain patient populations and requires clinical management.

Biological Activity and Therapeutic Uses

The compounds of the invention, and subgroups thereof, have fibroblast growth factor receptor (FGFR) inhibiting or modulating activity and/or vascular endothelial growth factor receptor (VEGFR) inhibiting or modulating activity, and/or platelet derived growth factor receptor (PDGFR) inhibiting or modulating activity, and which will be useful in preventing or treating disease states or conditions described herein. In addition the compounds of the invention, and subgroups thereof, will be useful in preventing or treating diseases or condition mediated by the kinases. References to the preventing or prophylaxis or treatment of a disease state or condition such as cancer include within their scope alleviating or reducing the incidence of cancer.

As used herein, the term "modulation", as applied to the activity of a kinase, is intended to define a change in the level of biological activity of the protein kinase. Thus, modulation encompasses physiological changes which effect an increase or decrease in the relevant protein kinase activity. In the latter case, the modulation may be described as "inhibition". The modulation may arise directly or indirectly, and may be mediated by any mechanism and at any physiological level, including for example at the level of gene expression (including for example transcription, translation and/or post-translational modification), at the level of expression of genes encoding regulatory elements which act directly or indirectly on the levels of kinase activity. Thus, modulation may imply elevated/suppressed expression or over- or under-expression of a kinase, including gene amplification (i.e. multiple gene copies) and/or increased or decreased expression by a transcriptional effect, as well as hyper- (or hypo-)activity and (de)activation of the protein kinase(s) (including (de)activation) by mutation(s). The terms "modulated", "modulating" and "modulate" are to be interpreted accordingly.

As used herein, the term "mediated", as used e.g. in conjunction with a kinase as described herein (and applied for example to various physiological processes, diseases, states, conditions, therapies, treatments or interventions) is intended to operate limitatively so that the various processes, diseases, states, conditions, treatments and interventions to which the term is applied are those in which the kinase plays a biological role. In cases where the term is applied to a disease, state or condition, the biological role played by a kinase may be direct or indirect and may be necessary and/or sufficient for the manifestation of the symptoms of the disease, state or condition (or its aetiology or progression). Thus, kinase activity (and in particular aberrant levels of kinase activity, e.g. kinase over-expression) need not necessarily be the proximal cause of the disease, state or condition: rather, it is contemplated that the kinase mediated diseases, states or conditions include those having multifactorial aetiologies and complex progressions in which the kinase in question is only partially involved. In cases where the term is applied to treatment, prophylaxis or intervention, the role played by the kinase may be direct or indirect and may be necessary and/or sufficient for the operation of the treatment, prophylaxis or outcome of the intervention. Thus, a disease state or condition mediated by a kinase includes the development of resistance to any particular cancer drug or treatment.

Thus, for example, the compounds of the invention may be useful in alleviating or reducing the incidence of cancer.

More particularly, the compounds of the formulae (I) and sub-groups thereof are inhibitors of FGFRs. For example, compounds of the invention have activity against FGFR1, FGFR2, FGFR3, and/or FGFR4, and in particular FGFRs selected from FGFR1, FGFR2 and FGFR3; or in particular the compounds of formula (I) and sub-groups thereof are inhibitors of FGFR4.

Preferred compounds are compounds that inhibit one or more FGFR selected from FGFR1, FGFR2, FGFR3, and FGFR4. Preferred compounds of the invention are those having IC_{50} values of less than 0.1 μM.

Compounds of the invention also have activity against VEGFR.

In addition many of the compounds of the invention exhibit selectivity for the FGFR 1, 2, and/or 3, and/or 4 compared to VEGFR (in particular VEGFR2) and/or PDGFR and such compounds represent one preferred embodiment of the invention. In particular, the compounds exhibit selectivity over VEGFR2. For example, many compounds of the invention have IC_{50} values against FGFR1, 2 and/or 3 and/or 4 that are between a tenth and a hundredth of the IC_{50} against VEGFR (in particular VEGFR2) and/or PDGFR B. In particular preferred compounds of the invention have at least 10 times greater activity against or inhibition of FGFR in particular FGFR1, FGFR2, FGFR3 and/or FGFR4 than VEGFR2. More preferably the compounds of the invention have at least 100 times greater activity against or inhibition of FGFR in particular FGFR1, FGFR2, FGFR3 and/or FGFR4 than VEGFR2. This can be determined using the methods described herein.

As a consequence of their activity in modulating or inhibiting FGFR, and/or VEGFR kinases, the compounds will be useful in providing a means of preventing the growth or inducing apoptosis of neoplasias, particularly by inhibiting angiogenesis. It is therefore anticipated that the compounds will prove useful in treating or preventing proliferative disorders such as cancers. In addition, the compounds of the invention could be useful in the treatment of diseases in which there is a disorder of proliferation, apoptosis or differentiation.

In particular tumours with activating mutants of VEGFR or upregulation of VEGFR and patients with elevated levels of serum lactate dehydrogenase may be particularly sensitive to the compounds of the invention. Patients with activating mutants of any of the isoforms of the specific RTKs discussed herein may also find treatment with the compounds of the invention particularly beneficial. For example, VEGFR overexpression in acute leukemia cells where the clonal progenitor may express VEGFR. Also, particular tumours with activating mutants or upregulation or overexpression of any of the isoforms of FGFR such as FGFR1, FGFR2 or FGFR3 or FGFR4 may be particularly sensitive to the compounds of the invention and thus patients as discussed herein with such particular tumours may also find treatment with the compounds of the invention particularly beneficial. It may be preferred that the treatment is related to or directed at a mutated form of one of the receptor tyrosine kinases, such as discussed herein. Diagnosis of tumours with such mutations could be performed using techniques known to a person skilled in the art and as described herein such as RTPCR and FISH.

Examples of cancers which may be treated (or inhibited) include, but are not limited to, a carcinoma, for example a carcinoma of the bladder, breast, colon (e.g. colorectal carcinomas such as colon adenocarcinoma and colon adenoma), kidney, urothelial, uterus, epidermis, liver, lung (for example adenocarcinoma, small cell lung cancer and non-small cell lung carcinomas, squamous lung cancer), oesophagus, head and neck, gall bladder, ovary, pancreas (e.g. exocrine pancreatic carcinoma), stomach, gastrointestinal (also known as gastric) cancer (e.g. gastrointestinal stromal tumours), cervix, endometrium, thyroid, prostate, or skin (for example squamous cell carcinoma or dermatofibrosarcoma protuberans); pituitary cancer, a hematopoietic tumour of lymphoid lineage, for example leukemia, acute lymphocytic leukemia, chronic lymphocytic leukemia, B-cell lymphoma (e.g. diffuse large B-cell lymphoma), T-cell lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, hairy cell lymphoma, or Burkett's lymphoma; a hematopoietic tumour of myeloid lineage, for example leukemias, acute and chronic myelogenous leukemias, chronic myelomonocytic leukemia (CMML), myeloproliferative disorder, myeloproliferative syndrome, myelodysplastic syndrome, or promyelocytic leukemia; multiple myeloma; thyroid follicular cancer; hepatocellular cancer, a tumour of mesenchymal origin (e.g. Ewing's sarcoma), for example fibrosarcoma or rhabdomyosarcoma; a tumour of the central or peripheral nervous system, for example astrocytoma, neuroblastoma, glioma (such as glioblastoma multiforme) or schwannoma; melanoma; seminoma; teratocarcinoma; osteosarcoma; xeroderma pigmentosum; keratoctanthoma; thyroid follicular cancer; or Kaposi's sarcoma. In particular, squamous lung cancer, breast cancer, colorectal cancer, glioblastoma, astrocytomas, prostate cancer, small cell lung cancer, melanoma, head and neck cancer, thyroid cancer, uterine cancer, gastric cancer, hepatocellular cancer, cervix cancer, multiple myeloma, bladder cancer, endometrial cancer, urothelial cancer, colon cancer, rhabdomyosarcoma, pituitary gland cancer.

Certain cancers are resistant to treatment with particular drugs. This can be due to the type of the tumour or can arise due to treatment with the compound. In this regard, references to multiple myeloma includes bortezomib sensitive multiple myeloma or refractory multiple myeloma. Similarly, references to chronic myelogenous leukemia includes imitanib sensitive chronic myelogenous leukemia and refractory chronic myelogenous leukemia. Chronic myelogenous leukemia is also known as chronic myeloid leukemia, chronic granulocytic leukemia or CML. Likewise, acute myelogenous leukemia, is also called acute myeloblastic leukemia, acute granulocytic leukemia, acute nonlymphocytic leukaemia or AML.

The compounds of the invention can also be used in the treatment of hematopoetic diseases of abnormal cell proliferation whether pre-malignant or stable such as myeloproliferative diseases. Myeloproliferative diseases ("MPD"s) are a group of diseases of the bone marrow in which excess cells are produced. They are related to, and may evolve into, myelodysplastic syndrome. Myeloproliferative diseases include polycythemia vera, essential thrombocythemia and primary myelofibrosis. A further haematological disorder is hypereosinophilic syndrome. T-cell lymphoproliferative diseases include those derived from natural Killer cells.

In addition the compounds of the invention can be used to gastrointestinal (also known as gastric) cancer e.g. gastrointestinal stromal tumours. Gastrointestinal cancer refers to malignant conditions of the gastrointestinal tract, including the esophagus, stomach, liver, biliary system, pancreas, bowels, and anus.

Thus, in the pharmaceutical compositions, uses or methods of this invention for treating a disease or condition comprising abnormal cell growth, the disease or condition comprising abnormal cell growth in one embodiment is a cancer.

Particular subsets of cancers include multiple myeloma, bladder, cervical, prostate and thyroid carcinomas, lung, breast, and colon cancers.

A further subset of cancers includes multiple myeloma, bladder, hepatocellular, oral squamous cell carcinoma and cervical carcinomas.

The compound of the invention, having FGFR such as FGFR1 inhibitory activity, may be particularly useful in the treatment or prevention of breast cancer in particular Classic Lobular Carcinomas (CLC).

As the compounds of the invention have FGFR4 activity they will also be useful in the treatment of prostate or pituitary cancers, or they will be useful in the treatment of breast cancer, lung cancer, prostate cancer, liver cancer (HCC) or lung cancer.

In particular the compounds of the invention as FGFR inhibitors, are useful in the treatment of multiple myeloma, myeloproliferatoive disorders, endometrial cancer, prostate cancer, bladder cancer, lung cancer, ovarian cancer, breast cancer, gastric cancer, colorectal cancer, and oral squamous cell carcinoma.

Further subsets of cancer are multiple myeloma, endometrial cancer, bladder cancer, cervical cancer, prostate cancer, lung cancer, breast cancer, colorectal cancer and thyroid carcinomas.

In particular the compounds of the invention are useful in the treatment of multiple myeloma (in particular multiple myeloma with t(4; 14) translocation or overexpressing FGFR3), prostate cancer (hormone refractory prostrate carcinomas), endometrial cancer (in particular endometrial tumours with activating mutations in FGFR2) and breast cancer (in particular lobular breast cancer).

In particular the compounds are useful in the treatment of lobular carcinomas such as CLC (Classic lobular carcinoma).

As the compounds have activity against FGFR3 they will be useful in the treatment of multiple myeloma and bladder cancer.

In particular the compounds are useful for the treatment of t(4; 14) translocation positive multiple myeloma.

In one embodiment the compounds may be useful for the treatment of sarcoma. In one embodiment the compounds may be useful for the treatment of lung cancer, e.g. squamous cell carcinoma.

As the compounds have activity against FGFR2 they will be useful in the treatment of endometrial, ovarian, gastric, hepatocellular, uterine, cervix and colorectal cancers. FGFR2 is also overexpressed in epithelial ovarian cancer, therefore the compounds of the invention may be specifically useful in treating ovarian cancer such as epithelial ovarian cancer.

In one embodiment, the compounds may be useful for the treatment of lung cancer, in particular NSCLC, squamous cell carcinoma, liver cancer, kidney cancer, breast cancer, colon cancer, colorectal cancer, prostate cancer.

In one embodiment, the compounds may be useful for the treatment of prostate cancer, bladder cancer, lung cancer such as NSCLC, breast cancer, gastric cancer, and liver cancer (HCC (hepatocellular cancer)).

Compounds of the invention may also be useful in the treatment of tumours pre-treated with VEGFR2 inhibitor or VEGFR2 antibody (e.g. Avastin).

In particular the compounds of the invention may be useful in the treatment of VEGFR2-resistant tumours. VEGFR2 inhibitors and antibodies are used in the treatment of thyroid and renal cell carcinomas, therefore the compounds of the invention may be useful in the treatment of VEGFR2-resistant thyroid and renal cell carcinomas.

The cancers may be cancers which are sensitive to inhibition of any one or more FGFRs selected from FGFR1, FGFR2, FGFR3, FGFR4, for example, one or more FGFRs selected from FGFR1, FGFR2 or FGFR3.

Whether or not a particular cancer is one which is sensitive to inhibition of FGFR or VEGFR signalling may be determined by means of a cell growth assay as set out below or by a method as set out in the section headed "Methods of Diagnosis".

The compounds of the invention, and in particular those compounds having FGFR, or VEGFR inhibitory activity, may be particularly useful in the treatment or prevention of cancers of a type associated with or characterised by the presence of elevated levels of FGFR, or VEGFR, for example the cancers referred to in this context in the introductory section of this application.

The compounds of the present invention may be useful for the treatment of the adult population. The compounds of the present invention may be useful for the treatment of the pediatric population.

It has been discovered that some FGFR inhibitors can be used in combination with other anticancer agents. For example, it may be beneficial to combine an inhibitor that induces apoptosis with another agent which acts via a different mechanism to regulate cell growth thus treating two of the characteristic features of cancer development. Examples of such combinations are set out below.

The compounds of the invention may be useful in treating other conditions which result from disorders in proliferation such as type II or non-insulin dependent diabetes mellitus, autoimmune diseases, head trauma, stroke, epilepsy, neurodegenerative diseases such as Alzheimer's, motor neurone disease, progressive supranuclear palsy, corticobasal degeneration and Pick's disease for example autoimmune diseases and neurodegenerative diseases.

One sub-group of disease states and conditions that the compounds of the invention may be useful consists of inflammatory diseases, cardiovascular diseases and wound healing.

FGFR, and VEGFR are also known to play a role in apoptosis, angiogenesis, proliferation, differentiation and transcription and therefore the compounds of the invention could also be useful in the treatment of the following diseases other than cancer; chronic inflammatory diseases, for example systemic lupus erythematosus, autoimmune mediated glomerulonephritis, rheumatoid arthritis, psoriasis, inflammatory bowel disease, autoimmune diabetes mellitus, Eczema hypersensitivity reactions, asthma, COPD, rhinitis, and upper respiratory tract disease; cardiovascular diseases for example cardiac hypertrophy, restenosis, atherosclerosis; neurodegenerative disorders, for example Alzheimer's disease, AIDS-related dementia, Parkinson's disease, amyotropic lateral sclerosis, retinitis pigmentosa, spinal muscular atropy and cerebellar degeneration; glomerulonephritis; myelodysplastic syndromes, ischemic injury associated myocardial infarctions, stroke and reperfusion injury, arrhythmia, atherosclerosis, toxin-induced or alcohol related liver diseases, haematological diseases, for example, chronic anemia and aplastic anemia; degenerative diseases of the musculoskeletal system, for example, osteoporosis and arthritis, aspirin-sensitive rhinosinusitis, cystic fibrosis, multiple sclerosis, kidney diseases and cancer pain.

In addition, mutations of FGFR2 are associated with several severe abnormalities in human skeletal development and thus the compounds of invention could be useful in the treatment of abnormalities in human skeletal development, including abnormal ossification of cranial sutures (craniosynostosis), Apert (AP) syndrome, Crouzon syndrome, Jackson-Weiss syndrome, Beare-Stevenson cutis gyrate syndrome, and Pfeiffer syndrome.

The compound of the invention, having FGFR such as FGFR2 or FGFR3 inhibitory activity, may be particularly useful in the treatment or prevention of the skeletal diseases. Particular skeletal diseases are achondroplasia or thanatophoric dwarfism (also known as thanatophoric dysplasia).

The compound of the invention, having FGFR such as FGFR1, FGFR2 or FGFR3 inhibitory activity, may be particularly useful in the treatment or prevention in pathologies in which progressive fibrosis is a symptom. Fibrotic conditions in which the compounds of the inventions may be useful in the treatment of include diseases exhibiting abnormal or excessive deposition of fibrous tissue for example in liver cirrhosis, glomerulonephritis, pulmonary fibrosis, systemic fibrosis, rheumatoid arthritis, as well as the natural process of wound healing. In particular the compounds of the inventions may also be useful in the treatment of lung fibrosis in particular in idiopathic pulmonary fibrosis.

The over-expression and activation of FGFR and VEGFR in tumor-associated vasculature has also suggested a role for compounds of the invention in preventing and disrupting initiation of tumor angiogenesis. In particular the compounds of the invention may be useful in the treatment of cancer, metastasis, leukemia's such as CLL, ocular diseases such as age-related macular degeneration in particular wet form of age-related macular degeneration, ischemic proliferative retinopathies such as retinopathy of prematurity (ROP) and diabetic retinopathy, rheumatoid arthritis and hemangioma.

The activity of the compounds of the invention as inhibitors of FGFR1-4, VEGFR and/or PDGFR A/B can be measured using the assays set forth in the examples below and the level of activity exhibited by a given compound can be defined in terms of the IC_{50} value. Preferred compounds of the present invention are compounds having an IC_{50} value of less than 1 μM, more preferably less than 0.1 μM.

The invention provides compounds that have FGFR inhibiting or modulating activity, and which may be useful in preventing or treating disease states or conditions mediated by FGFR kinases.

In one embodiment, there is provided a compound as defined herein for use in therapy, for use as a medicine. In a further embodiment, there is provided a compound as defined herein for use in the prophylaxis or treatment, in particular in the treatment, of a disease state or condition mediated by a FGFR kinase.

Thus, for example, the compounds of the invention may be useful in alleviating or reducing the incidence of cancer. Therefore, in a further embodiment, there is provided a compound as defined herein for use in the prophylaxis or treatment, in particular the treatment, of cancer. In one embodiment, the compound as defined herein is for use in the prophylaxis or treatment of FGFR-dependent cancer. In one embodiment, the compound as defined herein is for use in the prophylaxis or treatment of cancer mediated by FGFR kinases.

Accordingly, the invention provides inter alia:

A method for the prophylaxis or treatment of a disease state or condition mediated by a FGFR kinase, which method comprises administering to a subject in need thereof a compound of the formula (I) as defined herein.

A method for the prophylaxis or treatment of a disease state or condition as described herein, which method comprises administering to a subject in need thereof a compound of the formula (I) as defined herein.

A method for the prophylaxis or treatment of cancer, which method comprises administering to a subject in need thereof a compound of the formula (I) as defined herein.

A method for alleviating or reducing the incidence of a disease state or condition mediated by a FGFR kinase, which method comprises administering to a subject in need thereof a compound of the formula (I) as defined herein.

A method of inhibiting a FGFR kinase, which method comprises contacting the kinase with a kinase-inhibiting compound of the formula (I) as defined herein.

A method of modulating a cellular process (for example cell division) by inhibiting the activity of a FGFR kinase using a compound of the formula (I) as defined herein.

A compound of formula (I) as defined herein for use as a modulator of a cellular process (for example cell division) by inhibiting the activity of a FGFR kinase.

A compound of formula (I) as defined herein for use in the prophylaxis or treatment of cancer, in particular the treatment of cancer.

A compound of formula (I) as defined herein for use as a modulator (e.g. inhibitor) of FGFR.

The use of a compound of formula (I) as defined herein for the manufacture of a medicament for the prophylaxis or treatment of a disease state or condition mediated by a FGFR kinase, the compound having the formula (I) as defined herein.

The use of a compound of formula (I) as defined herein for the manufacture of a medicament for the prophylaxis or treatment of a disease state or condition as described herein.

The use of a compound of formula (I) as defined herein for the manufacture of a medicament for the prophylaxis or treatment, in particular the treatment, of cancer.

The use of a compound of formula (I) as defined herein for the manufacture of a medicament for modulating (e.g. inhibiting) the activity of FGFR.

Use of a compound of formula (I) as defined herein in the manufacture of a medicament for modulating a cellular process (for example cell division) by inhibiting the activity of a FGFR kinase.

The use of a compound of the formula (I) as defined herein for the manufacture of a medicament for prophylaxis or treatment of a disease or condition characterised by up-regulation of a FGFR kinase (e.g. FGFR1 or FGFR2 or FGFR3 or FGFR4).

The use of a compound of the formula (I) as defined herein for the manufacture of a medicament for the prophylaxis or treatment of a cancer, the cancer being one which is characterised by up-regulation of a FGFR kinase (e.g. FGFR1 or FGFR2 or FGFR3 or FGFR4).

The use of a compound of the formula (I) as defined herein for the manufacture of a medicament for the prophylaxis or treatment of cancer in a patient selected from a sub-population possessing a genetic aberrations of FGFR3 kinase.

The use of a compound of the formula (I) as defined herein for the manufacture of a medicament for the prophylaxis or treatment of cancer in a patient who has been diagnosed as forming part of a sub-population possessing a genetic aberrations of FGFR3 kinase.

A method for the prophylaxis or treatment of a disease or condition characterised by up-regulation of a FGFR kinase (e.g. FGFR1 or FGFR2 or FGFR3 or FGFR4), the method comprising administering a compound of the formula (I) as defined herein.

A method for alleviating or reducing the incidence of a disease or condition characterised by up-regulation of a FGFR kinase (e.g. FGFR1 or FGFR2 or FGFR3 or FGFR4), the method comprising administering a compound of the formula (I) as defined herein.

A method for the prophylaxis or treatment of (or alleviating or reducing the incidence of) cancer in a patient suffering from or suspected of suffering from cancer; which method comprises (i) subjecting a patient to a diagnostic test to determine whether the patient possesses a genetic aberrations of FGFR3 gene; and (ii) where the patient does possess the said variant, thereafter administering to the patient a compound of the formula (I) as defined herein having FGFR3 kinase inhibiting activity.

A method for the prophylaxis or treatment of (or alleviating or reducing the incidence of) a disease state or condition characterised by up-regulation of an FGFR kinase (e.g. FGFR1 or FGFR2 or FGFR3 or FGFR4); which method comprises (i) subjecting a patient to a diagnostic test to detect a marker characteristic of up-regulation of a FGFR kinase (e.g. FGFR1 or FGFR2 or FGFR3 or FGFR4) and (ii) where the diagnostic test is indicative of up-regulation of a FGFR kinase, thereafter administering to the patient a compound of the formula (I) as defined herein having FGFR kinase inhibiting activity.

In one embodiment, the disease mediated by FGFR kinases is a oncology related disease (e.g. cancer). In one embodiment, the disease mediated by FGFR kinases is a non-oncology related disease (e.g. any disease disclosed herein excluding cancer). In one embodiment the disease mediated by FGFR kinases is a condition described herein. In one embodiment the disease mediated by FGFR kinases is a skeletal condition described herein. Particular abnormalities in human skeletal development, include abnormal ossification of cranial sutures (craniosynostosis), Apert (AP) syndrome, Crouzon syndrome, Jackson-Weiss syndrome, Beare-Stevenson cutis gyrate syndrome, Pfeiffer syndrome, achondroplasia and thanatophoric dwarfism (also known as thanatophoric dysplasia).

Mutated Kinases

Drug resistant kinase mutations can arise in patient populations treated with kinase inhibitors. These occur, in part, in the regions of the protein that bind to or interact with the particular inhibitor used in therapy. Such mutations reduce or increase the capacity of the inhibitor to bind to and inhibit the kinase in question. This can occur at any of the amino acid residues which interact with the inhibitor or are important for supporting the binding of said inhibitor to the target. An inhibitor that binds to a target kinase without requiring the interaction with the mutated amino acid residue will likely be unaffected by the mutation and will remain an effective inhibitor of the enzyme.

A study in gastric cancer patient samples showed the presence of two mutations in FGFR2, Ser167Pro in exon IIIa and a splice site mutation 940-2A-G in exon IIIc. These mutations are identical to the germline activating mutations that cause craniosynotosis syndromes and were observed in 13% of primary gastric cancer tissues studied. In addition activating mutations in FGFR3 were observed in 5% of the patient samples tested and overexpression of FGFRs has been correlated with a poor prognosis in this patient group.

In addition there are chromosomal translocations or point mutations that have been observed in FGFR which give rise to gain-of-function, over-expressed, or constitutively active biological states.

The compounds of the invention would therefore find particular application in relation to cancers which express a mutated molecular target such as FGFR. Diagnosis of tumours with such mutations could be performed using techniques known to a person skilled in the art and as described herein such as RTPCR and FISH.

It has been suggested that mutations of a conserved threonine residue at the ATP binding site of FGFR would result in inhibitor resistance. The amino acid valine 561 has been mutated to a methionine in FGFR1 which corresponds to previously reported mutations found in Abl (T315) and EGFR (T766) that have been shown to confer resistance to selective inhibitors. Assay data for FGFR1 V561M showed that this mutation conferred resistance to a tyrosine kinase inhibitor compared to that of the wild type.

Methods of Diagnosis

Prior to administration of a compound of the formula (I), a patient may be screened to determine whether a disease or condition from which the patient is or may be suffering is one which would be susceptible to treatment with a compound having activity against FGFR, and/or VEGFR.

For example, a biological sample taken from a patient may be analysed to determine whether a condition or disease, such as cancer, that the patient is or may be suffering from is one which is characterised by a genetic abnormality or abnormal protein expression which leads to up-regulation of the levels or activity of FGFR, and/or VEGFR or to sensitisation of a pathway to normal FGFR, and/or VEGFR activity, or to upregulation of these growth factor signalling pathways such as growth factor ligand levels or growth factor ligand activity or to upregulation of a biochemical pathway downstream of FGFR, and/or VEGFR activation.

Examples of such abnormalities that result in activation or sensitisation of the FGFR, and/or VEGFR signal include loss of, or inhibition of apoptotic pathways, up-regulation of the receptors or ligands, or presence of mutant variants of the receptors or ligands e.g PTK variants. Tumours with mutants of FGFR1, FGFR2 or FGFR3 or FGFR4 or up-regulation, in particular over-expression of FGFR1, or gain-of-function mutants of FGFR2 or FGFR3 may be particularly sensitive to FGFR inhibitors.

For example, point mutations engendering gain-of-function in FGFR2 have been identified in a number of conditions. In particular activating mutations in FGFR2 have been identified in 10% of endometrial tumours.

In addition, genetic aberrations of the FGFR3 receptor tyrosine kinase such as chromosomal translocations or point mutations resulting in ectopically expressed or deregulated, constitutively active, FGFR3 receptors have been identified and are linked to a subset of multiple myelomas, bladder and cervical carcinomas. A particular mutation T6741 of the PDGF receptor has been identified in imatinib-treated patients. In addition, a gene amplification of 8p12-p11.2 was demonstrated in ~50% of lobular breast cancer (CLC) cases and this was shown to be linked with an increased expression of FGFR1. Preliminary studies with siRNA directed against FGFR1, or a small molecule inhibitor of the receptor, showed cell lines harbouring this amplification to be particularly sensitive to inhibition of this signalling pathway.

Alternatively, a biological sample taken from a patient may be analysed for loss of a negative regulator or suppressor of FGFR or VEGFR. In the present context, the term "loss" embraces the deletion of a gene encoding the regulator or suppressor, the truncation of the gene (for example by mutation), the truncation of the transcribed product of the gene, or the inactivation of the transcribed product (e.g. by point mutation) or sequestration by another gene product.

The term up-regulation includes elevated expression or over-expression, including gene amplification (i.e. multiple gene copies) and increased expression by a transcriptional effect, and hyperactivity and activation, including activation by mutations. Thus, the patient may be subjected to a diagnostic test to detect a marker characteristic of up-regulation of FGFR, and/or VEGFR. The term diagnosis includes screening. By marker we include genetic markers including, for example, the measurement of DNA composition to identify mutations of FGFR, and/or VEGFR. The term marker also includes markers which are characteristic of up regulation of FGFR and/or VEGFR, including enzyme activity, enzyme levels, enzyme state (e.g. phosphorylated or not) and mRNA levels of the aforementioned proteins.

The diagnostic tests and screens are typically conducted on a biological sample selected from tumour biopsy samples, blood samples (isolation and enrichment of shed tumour cells), stool biopsies, sputum, chromosome analysis, pleural fluid, peritoneal fluid, buccal spears, biopsy or urine.

Methods of identification and analysis of mutations and up-regulation of proteins are known to a person skilled in the art. Screening methods could include, but are not limited to, standard methods such as reverse-transcriptase polymerase chain reaction (RT-PCR) or in-situ hybridization such as fluorescence in situ hybridization (FISH).

Identification of an individual carrying a mutation in FGFR, and/or VEGFR may mean that the patient would be particularly suitable for treatment with a FGFR, and/or VEGFR inhibitor. Tumours may preferentially be screened for presence of a FGFR, and/or VEGFR variant prior to treatment. The screening process will typically involve direct sequencing, oligonucleotide microarray analysis, or a mutant specific antibody. In addition, diagnosis of tumours with such mutations could be performed using techniques known to a person skilled in the art and as described herein such as RT-PCR and FISH.

In addition, mutant forms of, for example FGFR or VEGFR2, can be identified by direct sequencing of, for example, tumour biopsies using PCR and methods to sequence PCR products directly as hereinbefore described. The skilled artisan will recognize that all such well-known techniques for detection of the over expression, activation or mutations of the aforementioned proteins could be applicable in the present case.

In screening by RT-PCR, the level of mRNA in the tumour is assessed by creating a cDNA copy of the mRNA followed by amplification of the cDNA by FOR. Methods of PCR amplification, the selection of primers, and conditions for amplification, are known to a person skilled in the art. Nucleic acid manipulations and PCR are carried out by standard methods, as described for example in Ausubel, F. M. et al., eds. (2004) Current Protocols in Molecular Biology, John Wiley & Sons Inc., or Innis, M. A. et al., eds. (1990) PCR Protocols: a guide to methods and applications, Academic Press, San Diego. Reactions and manipulations involving nucleic acid techniques are also described in Sambrook at al., (2001), 3rd Ed, Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratory Press. Alternatively a commercially available kit for RT-PCR (for example Roche Molecular Biochemicals) may be used, or methodology as set forth in U.S. Pat. Nos. 4,666,828; 4,683,202; 4,801,531; 5,192,659, 5,272,057, 5,882,864, and 6,218,529 and incorporated herein by reference. An example of an in-situ hybridisation technique for assessing mRNA expression would be fluorescence in-situ hybridisation (FISH) (see Angerer (1987) Meth. Enzymol., 152: 649).

Generally, in situ hybridization comprises the following major steps: (1) fixation of tissue to be analyzed; (2) prehybridization treatment of the sample to increase accessibility of target nucleic acid, and to reduce nonspecific binding; (3) hybridization of the mixture of nucleic acids to the nucleic acid in the biological structure or tissue; (4) post-hybridization washes to remove nucleic acid fragments not bound in the hybridization, and (5) detection of the hybridized nucleic acid fragments. The probes used in such applications are typically labelled, for example, with radioisotopes or fluorescent reporters. Preferred probes are sufficiently long, for example, from about 50, 100, or 200 nucleotides to about 1000 or more nucleotides, to enable specific hybridization with the target nucleic acid(s) under stringent conditions. Standard methods for carrying out FISH are described in Ausubel, F. M. et al., eds. (2004) Current Protocols in Molecular Biology, John Wiley & Sons Inc and Fluorescence In Situ Hybridization: Technical Overview by John M. S. Bartlett in Molecular Diagnosis of Cancer, Methods and

Protocols, 2nd ed.; ISBN: 1-59259-760-2; March 2004, pps. 077-088; Series: Methods in Molecular Medicine.

Methods for gene expression profiling are described by (DePrimo et al. (2003), *BMC Cancer,* 3:3). Briefly, the protocol is as follows: double-stranded cDNA is synthesized from total RNA Using a (dT)24 oligomer for priming first-strand cDNA synthesis, followed by second strand cDNA synthesis with random hexamer primers. The double-stranded cDNA is used as a template for in vitro transcription of cRNA using biotinylated ribonucleotides. cRNA is chemically fragmented according to protocols described by Affymetrix (Santa Clara, Calif., USA), and then hybridized overnight on Human Genome Arrays.

Alternatively, the protein products expressed from the mRNAs may be assayed by immunohistochemistry of tumour samples, solid phase immunoassay with microtitre plates, Western blotting, 2-dimensional SDS-polyacrylamide gel electrophoresis, ELISA, flow cytometry and other methods known in the art for detection of specific proteins. Detection methods would include the use of site specific antibodies. The skilled person will recognize that all such well-known techniques for detection of upregulation of FGFR, and/or VEGFR, or detection of FGFR, and/or VEGFR variants or mutants could be applicable in the present case.

Abnormal levels of proteins such as FGFR or VEGFR can be measured using standard enzyme assays, for example, those assays described herein. Activation or overexpression could also be detected in a tissue sample, for example, a tumour tissue. By measuring the tyrosine kinase activity with an assay such as that from Chemicon International. The tyrosine kinase of interest would be immunoprecipitated from the sample lysate and its activity measured.

Alternative methods for the measurement of the over expression or activation of FGFR or VEGFR including the isoforms thereof, include the measurement of microvessel density. This can for example be measured using methods described by Orre and Rogers (Int J Cancer (1999), 84(2) 101-8). Assay methods also include the use of markers, for example, in the case of VEGFR these include CD31, CD34 and CD105.

Therefore all of these techniques could also be used to identify tumours particularly suitable for treatment with the compounds of the invention.

The compounds of the invention are particular useful in treatment of a patient having a mutated FGFR. The G697C mutation in FGFR3 is observed in 62% of oral squamous cell carcmonas and causes constitutive activation of the kinase activity. Activating mutations of FGFR3 have also been identified in bladder carcinoma cases. These mutations were of 6 kinds with varying degrees of prevelence: R248C, S249C, G372C, S373C, Y375C, K652Q. In addition, a Gly388Arg polymorphism in FGFR4 has been found to be associated with increased incidence and aggressiveness of prostate, colon, lung, liver (HCC) and breast cancer.

Therefore in a further aspect the invention includes use of a compound according to the invention for the manufacture of a medicament for the treatment or prophylaxis of a disease state or condition in a patient who has been screened and has been determined as suffering from, or being at risk of suffering from, a disease or condition which would be susceptible to treatment with a compound having activity against FGFR.

Particular mutations a patient is screened for include G697C, R248C, S249C, G372C, S373C, Y375C, K652Q mutations in FGFR3 and Gly388Arg polymorphism in FGFR4.

In another aspect the invention includes a compound of the invention for use in the prophylaxis or treatment of cancer in a patient selected from a sub-population possessing a variant of the FGFR gene (for example G697C mutation in FGFR3 and Gly388Arg polymorphism in FGFR4).

MRI determination of vessel normalization (e.g. using MRI gradient echo, spin echo, and contrast enhancement to measure blood volume, relative vessel size, and vascular permeability) in combination with circulating biomarkers (circulating progenitor cells (CPCs), CECs, SDF1, and FGF2) may also be used to identify VEGFR2-resistant tumours for treatment with a compound of the invention.

Pharmaceutical Compositions and Combinations

In view of their useful pharmacological properties, the subject compounds may be formulated into various pharmaceutical forms for administration purposes.

In one embodiment the pharmaceutical composition (e.g. formulation) comprises at least one active compound of the invention together with one or more pharmaceutically acceptable carriers, adjuvants, excipients, diluents, fillers, buffers, stabilisers, preservatives, lubricants, or other materials well known to those skilled in the art and optionally other therapeutic or prophylactic agents.

To prepare the pharmaceutical compositions of this invention, an effective amount of a compound of the present invention, as the active ingredient is combined in intimate admixture with a pharmaceutically acceptable carrier, which carrier may take a wide variety of forms depending on the form of preparation desired for administration. The pharmaceutical compositions can be in any form suitable for oral, parenteral, topical, intranasal, ophthalmic, otic, rectal, intravaginal, or transdermal administration. These pharmaceutical compositions are desirably in unitary dosage form suitable, preferably, for administration orally, rectally, percutaneously, or by parenteral injection. For example, in preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed, such as, for example, water, glycols, oils, alcohols and the like in the case of oral liquid preparations such as suspensions, syrups, elixirs and solutions; or solid carriers such as starches, sugars, kaolin, lubricants, binders, disintegrating agents and the like in the case of powders, pills, capsules and tablets.

Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers are obviously employed. For parenteral compositions, the carrier will usually comprise sterile water, at least in large part, though other ingredients, to aid solubility for example, may be included. Injectable solutions, for example, may be prepared in which the carrier comprises saline solution, glucose solution or a mixture of saline and glucose solution. Injectable suspensions may also be prepared in which case appropriate liquid carriers, suspending agents and the like may be employed. In the compositions suitable for percutaneous administration, the carrier optionally comprises a penetration enhancing agent and/or a suitable wetting agent, optionally combined with suitable additives of any nature in minor proportions, which additives do not cause a significant deleterious effect to the skin. Said additives may facilitate the administration to the skin and/or may be helpful for preparing the desired compositions. These compositions may be administered in various ways, e.g., as a transdermal patch, as a spot-on, as an ointment. It is especially advantageous to formulate the aforementioned pharmaceutical compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used in the specification and claims herein refers to physically discrete units suitable as unitary dosages, each unit containing a predetermined quantity of active ingredient calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. Examples of such dosage unit forms are tablets (including scored or coated tablets), capsules, pills, powder packets, wafers, injectable solutions or suspensions, teaspoonfuls, tablespoonfuls and the like, and segregated multiples thereof.

It is especially advantageous to formulate the aforementioned pharmaceutical compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used in the specification and claims herein refers to physically discrete units suitable as unitary dosages, each unit containing a predetermined quantity of active ingredient, calculated to produce the desired therapeutic effect, in association with the required pharmaceutical carrier. Examples of such dosage unit forms are tablets (including scored or coated tablets), capsules, pills, powder packets, wafers, injectable solutions or suspensions, teaspoonfuls, tablespoonfuls and the like, and segregated multiples thereof.

The compound of the invention is administered in an amount sufficient to exert its anti-tumour activity.

Those skilled in the art could easily determine the effective amount from the test results presented hereinafter. In general it is contemplated that a therapeutically effective amount would be from 0.005 mg/kg to 100 mg/kg body weight, and in particular from 0.005 mg/kg to 10 mg/kg body weight. It may be appropriate to administer the required dose as single, two, three, four or more sub-doses at appropriate intervals throughout the day. Said sub-doses may be formulated as unit dosage forms, for example, containing 0.5 to 500 mg, in particular 1 mg to 500 mg, more in particular 10 mg to 500 mg of active ingredient per unit dosage form.

Depending on the mode of administration, the pharmaceutical composition will preferably comprise from 0.05 to 99% by weight, more preferably from 0.1 to 70% by weight, even more preferably from 0.1 to 50% by weight of the compound of the present invention, and, from 1 to 99.95% by weight, more preferably from 30 to 99.9% by weight, even more preferably from 50 to 99.9% by weight of a pharmaceutically acceptable carrier, all percentages being based on the total weight of the composition.

As another aspect of the present invention, a combination of a compound of the present invention with another anticancer agent is envisaged, especially for use as a medicine, more specifically for use in the treatment of cancer or related diseases.

For the treatment of the above conditions, the compounds of the invention may be advantageously employed in combination with one or more other medicinal agents, more particularly, with other anti-cancer agents or adjuvants in cancer therapy. Examples of anti-cancer agents or adjuvants (supporting agents in the therapy) include but are not limited to:

- platinum coordination compounds for example cisplatin optionally combined with amifostine, carboplatin or oxaliplatin;
- taxane compounds for example paclitaxel, paclitaxel protein bound particles (Abraxane™) or docetaxel;
- topoisomerase I inhibitors such as camptothecin compounds for example irinotecan, SN-38, topotecan, topotecan hcl;
- topoisomerase II inhibitors such as anti-tumour epipodophyllotoxins or podophyllotoxin derivatives for example etoposide, etoposide phosphate or teniposide;
- anti-tumour vinca alkaloids for example vinblastine, vincristine or vinorelbine;
- anti-tumour nucleoside derivatives for example 5-fluorouracil, leucovorin, gemcitabine, gemcitabine hcl, capecitabine, cladribine, fludarabine, nelarabine;
- alkylating agents such as nitrogen mustard or nitrosourea for example cyclophosphamide, chlorambucil, carmustine, thiotepa, mephalan (melphalan), lomustine, altretamine, busulfan, dacarbazine, estramustine, ifosfamide optionally in combination with mesna, pipobroman, procarbazine, streptozocin, telozolomide, uracil;

anti-tumour anthracycline derivatives for example daunorubicin, doxorubicin optionally in combination with dexrazoxane, doxil, idarubicin, mitoxantrone, epirubicin, epirubicin hcl, valrubicin;

molecules that target the IGF-1 receptor for example picropodophilin;

tetracarcin derivatives for example tetrocarcin A;

glucocorticoïden for example prednisone;

antibodies for example trastuzumab (HER2 antibody), rituximab (CD20 antibody), gemtuzumab, gemtuzumab ozogamicin, cetuximab, pertuzumab, bevacizumab, alemtuzumab, eculizumab, ibritumomab tiuxetan, nofetumomab, panitumumab, tositumomab, CNTO 328;

estrogen receptor antagonists or selective estrogen receptor modulators or inhibitors of estrogen synthesis for example tamoxifen, fulvestrant, toremifene, droloxifene, faslodex, raloxifene or letrozole;

aromatase inhibitors such as exemestane, anastrozole, letrazole, testolactone and vorozole;

differentiating agents such as retinoids, vitamin D or retinoic acid and retinoic acid metabolism blocking agents (RAMBA) for example accutane;

DNA methyl transferase inhibitors for example azacytidine or decitabine;

antifolates for example premetrexed disodium;

antibiotics for example antinomycin D, bleomycin, mitomycin C, dactinomycin, caminomycin, daunomycin, levamisole, plicamycin, mithramycin;

antimetabolites for example clofarabine, aminopterin, cytosine arabinoside or methotrexate, azacitidine, cytarabine, floxuridine, pentostatin, thioguanine;

apoptosis inducing agents and antiangiogenic agents such as Bcl-2 inhibitors for example YC 137, BH 312, ABT 737, gossypol, HA 14-1, TW 37 or decanoic acid;

tubuline-binding agents for example combrestatin, colchicines or nocodazole;

kinase inhibitors (e.g. EGFR (epithelial growth factor receptor) inhibitors, MTKI (multi target kinase inhibitors), mTOR inhibitors) for example flavoperidol, imatinib mesylate, erlotinib, gefitinib, dasatinib, lapatinib, lapatinib ditosylate, sorafenib, sunitinib, sunitinib maleate, temsirolimus;

farnesyltransferase inhibitors for example tipifarnib;

histone deacetylase (HDAC) inhibitors for example sodium butyrate, suberoylanilide hydroxamide acid (SAHA), depsipeptide (FR 901228), NVP-LAQ824, R306465, JNJ-26481585, trichostatin A, vorinostat;

Inhibitors of the ubiquitin-proteasome pathway for example PS-341, MLN 0.41 or bortezomib;

Yondelis;

Telomerase inhibitors for example telomestatin;

Matrix metalloproteinase inhibitors for example batimastat, marimastat, prinostat or metastat.

Recombinant interleukins for example aldesleukin, denileukin diftitox, interferon alfa 2a, interferon alfa 2b, peginterferon alfa 2b

MAPK inhibitors

Retinoids for example alitretinoin, bexarotene, tretinoin

Arsenic trioxide

Asparaginase

Steroids for example dromostanolone propionate, megestrol acetate, nandrolone (decanoate, phenpropionate), dexamethasone

Gonadotropin releasing hormone agonists or antagonists for example abarelix, goserelin acetate, histrelin acetate, leuprolide acetate

Thalidomide, lenalidomide

Mercaptopurine, mitotane, pamidronate, pegademase, pegaspargase, rasburicase

BH3 mimetics for example ABT-737

MEK inhibitors for example PD98059, AZD6244, CI-1040

colony-stimulating factor analogs for example filgrastim, pegfilgrastim, sargramostim; erythropoietin or analogues thereof (e.g. darbepoetin alfa); interleukin 11; oprelvekin; zoledronate, zoledronic acid; fentanyl; bisphosphonate; palifermin.

a steroidal cytochrome P450 17alpha-hydroxylase-17,20-lyase inhibitor (CYP17), e.g. abiraterone, abiraterone acetate.

The compounds of the present invention also have therapeutic applications in sensitising tumour cells for radiotherapy and chemotherapy.

Hence the compounds of the present invention can be used as “radiosensitizer” and/or “chemosensitizer” or can be given in combination with another “radiosensitizer” and/or “chemosensitizer”.

The term “radiosensitizer”, as used herein, is defined as a molecule, preferably a low molecular weight molecule, administered to animals in therapeutically effective amounts to increase the sensitivity of the cells to ionizing radiation and/or to promote the treatment of diseases which are treatable with ionizing radiation.

The term “chemosensitizer”, as used herein, is defined as a molecule, preferably a low molecular weight molecule, administered to animals in therapeutically effective amounts to increase the sensitivity of cells to chemotherapy and/or promote the treatment of diseases which are treatable with chemotherapeutics.

Several mechanisms for the mode of action of radiosensitizers have been suggested in the literature including: hypoxic cell radiosensitizers (e.g., 2-nitroimidazole compounds, and benzotriazine dioxide compounds) mimicking oxygen or alternatively behave like bioreductive agents under hypoxia; non-hypoxic cell radiosensitizers (e.g., halogenated pyrimidines) can be analogoues of DNA bases and preferentially incorporate into the DNA of cancer cells and thereby promote the radiation-induced breaking of DNA molecules and/or prevent the normal DNA repair mechanisms; and various other potential mechanisms of action have been hypothesized for radiosensitizers in the treatment of disease.

Many cancer treatment protocols currently employ radiosensitizers in conjunction with radiation of x-rays. Examples of x-ray activated radiosensitizers include, but are not limited to, the following: metronidazole, misonidazole, desmethylmisonidazole, pimonidazole, etanidazole, nimorazole, mitomycin C, RSU 1069, SR 4233, EO9, RB 6145, nicotinamide, 5-bromodeoxyuridine (BUdR), 5-iododeoxyuridine (IUdR), bromodeoxycytidine, fluorodeoxyuridine (FudR), hydroxyurea, cisplatin, and therapeutically effective analogs and derivatives of the same.

Photodynamic therapy (PDT) of cancers employs visible light as the radiation activator of the sensitizing agent. Examples of photodynamic radiosensitizers include the following, but are not limited to: hematoporphyrin derivatives, Photofrin, benzoporphyrin derivatives, tin etioporphyrin, pheoborbide-a, bacteriochlorophyll-a, naphthalocyanines, phthalocyanines, zinc phthalocyanine, and therapeutically effective analogs and derivatives of the same.

Radiosensitizers may be administered in conjunction with a therapeutically effective amount of one or more other compounds, including but not limited to: compounds which promote the incorporation of radiosensitizers to the target cells; compounds which control the flow of therapeutics, nutrients, and/or oxygen to the target cells; chemotherapeutic agents which act on the tumour with or without additional radiation; or other therapeutically effective compounds for treating cancer or other diseases.

Chemosensitizers may be administered in conjunction with a therapeutically effective amount of one or more other compounds, including but not limited to: compounds which promote the incorporation of chemosensitizers to the target cells; compounds which control the flow of therapeutics, nutrients, and/or oxygen to the target cells; chemotherapeutic agents which act on the tumour or other therapeutically effective compounds for treating cancer or other disease. Calcium antagonists, for example verapamil, are found useful in combination with antineoplastic agents to establish chemosensitivity in tumor cells resistant to accepted chemotherapeutic agents and to potentiate the efficacy of such compounds in drug-sensitive malignancies.

In view of their useful pharmacological properties, the components of the combinations according to the invention, i.e. the one or more other medicinal agent and the compound according to the present invention may be formulated into various pharmaceutical forms for administration purposes. The components may be formulated separately in individual pharmaceutical compositions or in a unitary pharmaceutical composition containing all components.

The present invention therefore also relates to a pharmaceutical composition comprising the one or more other medicinal agent and the compound according to the present invention together with a pharmaceutical carrier.

The present invention further relates to the use of a combination according to the invention in the manufacture of a pharmaceutical composition for inhibiting the growth of tumour cells.

The present invention further relates to a product containing as first active ingredient a compound according to the invention and as further active ingredient one or more anticancer agent, as a combined preparation for simultaneous, separate or sequential use in the treatment of patients suffering from cancer.

The one or more other medicinal agents and the compound according to the present invention may be administered simultaneously (e.g. in separate or unitary compositions) or sequentially in either order. In the latter case, the two or more compounds will be administered within a period and in an amount and manner that is sufficient to ensure that an advantageous or synergistic effect is achieved. It will be appreciated that the preferred method and order of administration and the respective dosage amounts and regimes for each component of the combination will depend on the particular other medicinal agent and compound of the present invention being administered, their route of administration, the particular tumour being treated and the particular host being treated. The optimum method and order of administration and the dosage amounts and regime can be readily determined by those skilled in the art using conventional methods and in view of the information set out herein.

The weight ratio of the compound according to the present invention and the one or more other anticancer agent(s) when given as a combination may be determined by the person skilled in the art. Said ratio and the exact dosage and frequency of administration depends on the particular compound according to the invention and the other anticancer agent(s) used, the particular condition being treated, the severity of the condition being treated, the age, weight, gender, diet, time of administration and general physical condition of the particular patient, the mode of administration as well as other medication the individual may be taking, as is well known to those skilled in the art.

Furthermore, it is evident that the effective daily amount may be lowered or increased depending on the response of the treated subject and/or depending on the evaluation of the physician prescribing the compounds of the instant invention. A particular weight ratio for the present compound of formula (I) and another anticancer agent may range from 1/10 to 10/1, more in particular from 1/5 to 5/1, even more in particular from 1/3 to 3/1.

The platinum coordination compound is advantageously administered in a dosage of 1 to 500 mg per square meter (mg/m^2) of body surface area, for example 50 to 400 mg/m^2, particularly for cisplatin in a dosage of about 75 mg/m^2 and for carboplatin in about 300 mg/m^2 per course of treatment.

The taxane compound is advantageously administered in a dosage of 50 to 400 mg per square meter (mg/m^2) of body surface area, for example 75 to 250 mg/m^2, particularly for paclitaxel in a dosage of about 175 to 250 mg/m^2 and for docetaxel in about 75 to 150 mg/m^2 per course of treatment.

The camptothecin compound is advantageously administered in a dosage of 0.1 to 400 mg per square meter (mg/m^2) of body surface area, for example 1 to 300 mg/m^2, particularly for irinotecan in a dosage of about 100 to 350 mg/m^2 and for topotecan in about 1 to 2 mg/m^2 per course of treatment.

The anti-tumour podophyllotoxin derivative is advantageously administered in a dosage of 30 to 300 mg per square meter (mg/m^2) of body surface area, for example 50 to 250 mg/m^2, particularly for etoposide in a dosage of about 35 to 100 mg/m^2 and for teniposide in about 50 to 250 mg/m^2 per course of treatment.

The anti-tumour vinca alkaloid is advantageously administered in a dosage of 2 to 30 mg per square meter (mg/m^2) of body surface area, particularly for vinblastine in a dosage of about 3 to 12 mg/m^2, for vincristine in a dosage of about 1 to 2 mg/m^2, and for vinorelbine in dosage of about 10 to 30 mg/m^2 per course of treatment.

The anti-tumour nucleoside derivative is advantageously administered in a dosage of 200 to 2500 mg per square meter (mg/m^2) of body surface area, for example 700 to 1500 mg/m^2, particularly for 5-FU in a dosage of 200 to 500 mg/m^2, for gemcitabine in a dosage of about 800 to 1200 mg/m^2 and for capecitabine in about 1000 to 2500 mg/m^2 per course of treatment.

The alkylating agents such as nitrogen mustard or nitrosourea is advantageously administered in a dosage of 100 to 500 mg per square meter (mg/m^2) of body surface area, for example 120 to 200 mg/m^2, particularly for cyclophosphamide in a dosage of about 100 to 500 mg/m^2, for chlorambucil in a dosage of about 0.1 to 0.2 mg/kg, for carmustine in a dosage of about 150 to 200 mg/m^2, and for lomustine in a dosage of about 100 to 150 mg/m^2 per course of treatment.

The anti-tumour anthracycline derivative is advantageously administered in a dosage of 10 to 75 mg per square meter (mg/m^2) of body surface area, for example 15 to 60 mg/m^2, particularly for doxorubicin in a dosage of about 40 to 75 mg/m^2, for daunorubicin in a dosage of about 25 to 45 mg/m^2, and for idarubicin in a dosage of about 10 to 15 mg/m^2 per course of treatment.

The antiestrogen agent is advantageously administered in a dosage of about 1 to 100 mg daily depending on the particular agent and the condition being treated. Tamoxifen is advantageously administered orally in a dosage of 5 to 50 mg, preferably 10 to 20 mg twice a day, continuing the therapy for sufficient time to achieve and maintain a therapeutic effect. Toremifene is advantageously administered orally in a dosage of about 60 mg once a day, continuing the therapy for sufficient time to achieve and maintain a therapeutic effect. Anastrozole is advantageously administered orally in a dosage of about 1 mg once a day. Droloxifene is advantageously administered orally in a dosage of about 20-100 mg once a day. Raloxifene is advantageously administered orally in a dosage of about 60 mg once a day. Exemestane is advantageously administered orally in a dosage of about 25 mg once a day.

Antibodies are advantageously administered in a dosage of about 1 to 5 mg per square meter (mg/m^2) of body surface area, or as known in the art, if different. Trastuzumab is advantageously administered in a dosage of 1 to 5 mg per square meter (mg/m^2) of body surface area, particularly 2 to 4 mg/m^2 per course of treatment. These dosages may be administered for example once, twice or more per course of treatment, which may be repeated for example every 7, 14, 21 or 28 days.

The compounds of formula (I), the pharmaceutically acceptable addition salts, in particular pharmaceutically acceptable acid addition salts, and stereoisomeric forms thereof can have valuable diagnostic properties in that they can be used for detecting or identifying the formation of a complex between a labelled compound and other molecules, peptides, proteins, enzymes or receptors.

The detecting or identifying methods can use compounds that are labelled with labelling agents such as radioisotopes, enzymes, fluorescent substances, luminous substances, etc. Examples of the radioisotopes include ^{125}I, ^{131}I, ^{3}H and ^{14}C. Enzymes are usually made detectable by conjugation of an appropriate substrate which, in turn catalyses a detectable reaction. Examples thereof include, for example, beta-galactosidase, beta-glucosidase, alkaline phosphatase, peroxidase and malate dehydrogenase, preferably horseradish peroxidase. The luminous substances include, for example, luminol, luminol derivatives, luciferin, aequorin and luciferase.

Biological samples can be defined as body tissue or body fluids. Examples of body fluids are cerebrospinal fluid, blood, plasma, serum, urine, sputum, saliva and the like.

General Synthetic Routes

The following examples illustrate the present invention but are examples only and are not intended to limit the scope of the claims in any way.

Experimental Part

Hereinafter, the term 'ACN' means acetonitrile, 'DOM' means dichloromethane, 'K_2CO_3' means potassium carbonate, '$MgSO_4$' means magnesium sulphate, 'MeOH' means methanol, 'EtOH' means ethanol, 'EtOAc' means ethyl acetate, 'Et_3N' means triethylamine, 'DIPE' means diisopropyl ether, 'THF' means tetrahydrofuran, 'NaH' means sodium hydride, 'NH_4OH' means ammonium hydroxide, 't-BuOH' means 2-methyl-2-propanol, 'Et_2O' means diethyl ether, 'SiOH' means silicium hydroxide, monosodium salt, 'MP' means melting point. 't-BuOMe' means 2-methyl-2-propyloxymethylether, '$NaHSO_3$' means sodiumhydrogenosulfite, DMF means dimethylormamide, XPhos means 2-Dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl, DME means dimethyl ether, Pd_2 dba_3 means Tris(dibenzylideneacetone)dipalladium(0), Xantphos means 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene, $NaHCO_3$ means sodium hydrogencarbonate, rt means room temperature, $PdCl_2$dppf means 1,1'-Bis(diphenylphosphino)ferrocene-palladium(II) dichloride, NaOtBu means sodium tertbutylate, Cs_2CO_3 means cesium carbonate, TBAF means tetrabutylammonium fluoride.

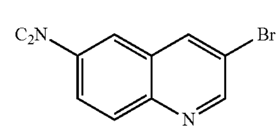
Some compounds of the present invention were obtained as salt forms or hydrates or contain some amounts of solvent. Hereinafter, these compounds are reported as determined based on elemental analysis.

A. Preparation of the Intermediates

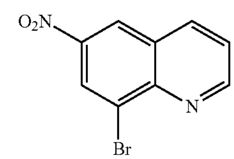
Example A1

a) Preparation of Intermediates 1 and 2

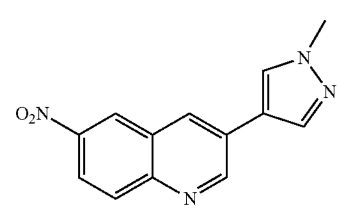
Interm. 1



Interm. 2



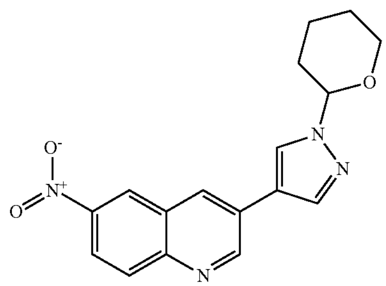
A solution of 6-nitroquinoline (28.1 g; 161 mmol) and N-bromosuccinimide (28.7 g; 161 mmol) in acetic acid (280 ml) was heated at 50° C. for 17 hours. The precipitate solid was filtered and washed with Et_2O, water and then Et_2O to afford 14.7 g g (27%) of intermediate 2 (purity 93%). The organic layer was evaporated to dryness and the residue was purified by chromatography over silica gel (mobile phase gradient from 50% petroleum ether, 50% DCM to 100% DCM). The pure fractions were collected and the solvent was evaporated, yielding 2.25 g (4%) of intermediate 2 and 16.6 g of a residue that was submitted to a second purification by chromatography over silica gel (mobile phase 50% petroleum9/1/0.2 cyclohexane/diethyl ether/DCM). The pure fractions were collected and the solvent was evaporated, yielding 14.1 g (28%) of intermediate 1.



b) Preparation of Intermediate 3

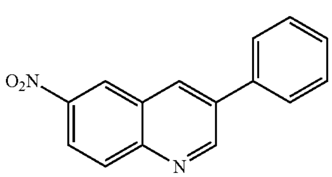
A solution of intermediate 1 (22 g; 86.5 mmol), 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (20 g, 95.5 mmol), an aqueous solution of sodium carbonate 2M (53 ml; 104 mmol) in ethylene glycol dimethyl ether (250 ml) were degassed with N_2 for 15 min. Tetrakis(triphenylphosphine)palladium0 (4 g; 3.5 mmol) was added and the mixture was refluxed for 18 hours. The reaction mixture was cooled down to room temperature, poured into water. The precipitate was filtered off and washed with water, with DIPE (twice), then diethylether and dried to afford 22 g of intermediate 3. Intermediate 3 was used without further purification for the next step.

Analogous preparation of intermediate 4



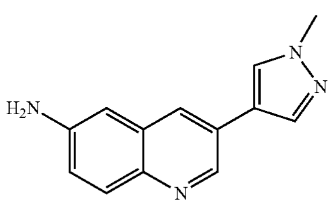
starting from intermediate 1

Analogous preparation of intermediate 33



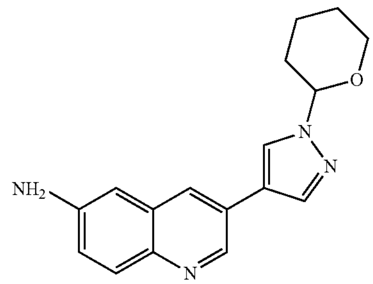
starting from intermediate 1

c) Preparation of Intermediate 5



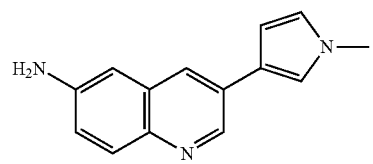
Intermediate 3(15 g; 59 mmol) was diluted in MeOH (200 ml) and THF (150 mL). Then, Raney Nickel (15 g) was added. The mixture was hydrogenated under pressure (3 bars) at room temperature for 1.5 hours. The mixture was filtered over a pad of Celite®, then washed with DCM and evaporated to dryness. The reaction was repeated on same amounts and combined residues (30 g) were purified by chromatography over silica gel (20-45 μm 1000 g, mobile phase gradient from 0.1% NH_4OH, 97% DCM, 3% MeOH to 0.1% NH_4OH, 95% DCM, 5% MeOH). The pure fractions were collected and the solvent was evaporated to afford 17 g (64%) of intermediate 5.

Analogous preparation of intermediate 6



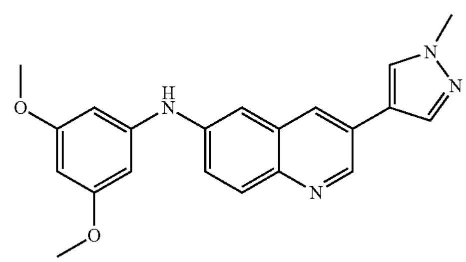
starting from intermediate 4

Analogous preparation of intermediate 47



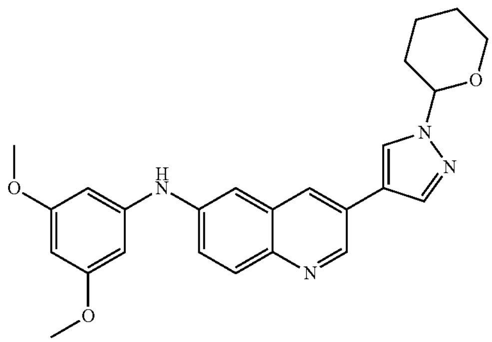
starting from intermediate 49

d) Preparation of Intermediate 7



A solution of intermediate 5 (10.5 g; 46.8 mmol), 1-bromo-3,5-dimethoxybenzene (10.1 g; 46.8 mmol), cesium carbonate (45.7 g; 140 mmol) and 2-dicyclohexylphosphino-2',4',6'-tri-i-propyl-1,1'-biphenyl (1.1 g; 2.3 mmol) in 2-methyl-2-propanol (280 ml) was degassed under N_2. Then tris(dibenzylideneacetone) dipalladium(0) (2.1 g; 2.3 mmol) was added and the mixture was stirred at 100° C. for 18 hours. The reaction mixture was diluted with MeOH and filtered over a pad of Celite® and washed with EtOAc. Water was added to the filtrate and the aquous layer was extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, filtered and evaporated. The crude product was taken up in Et_2O/CH_3CN, filtered and dried to give 7.9 g (46%) of intermediate 7.

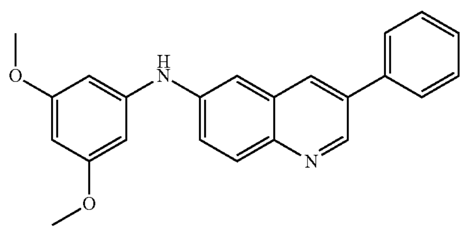
Analogous preparation of intermediate 8



starting from intermediate 6

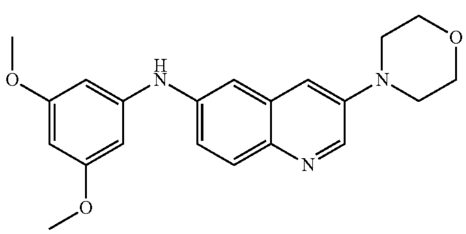
MS: $M^+(H^+)$: 431 (method 1, see analytical part)

Analogous preparation of intermediate 31



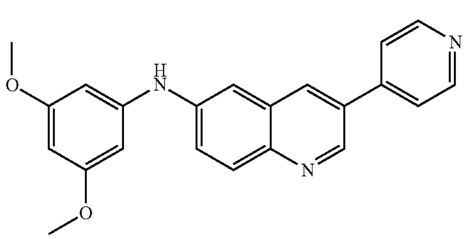
starting from intermediate 32

Analogous preparation of intermediate 36



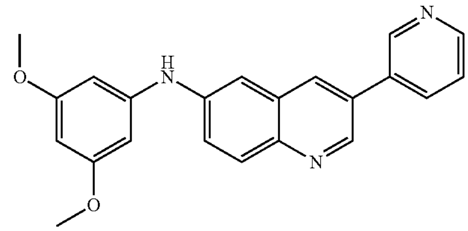
starting from intermediate 37

Analogous preparation of intermediate 39



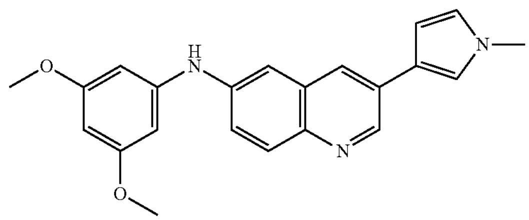
starting from intermediate 41

Analogous preparation of intermediate 42



starting from intermediate 43

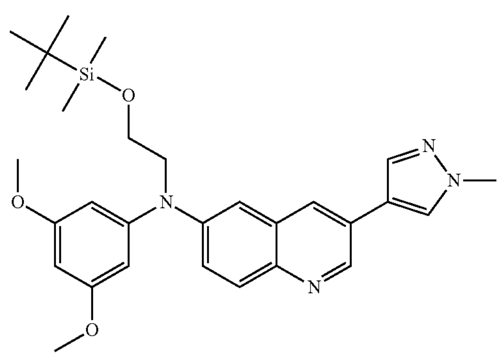
Analogous preparation of intermediate 46



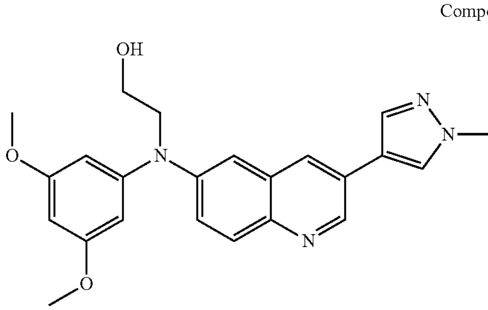
starting from intermediate 47

e) Preparation of Intermediate 9 and Compound 3

Interm. 9

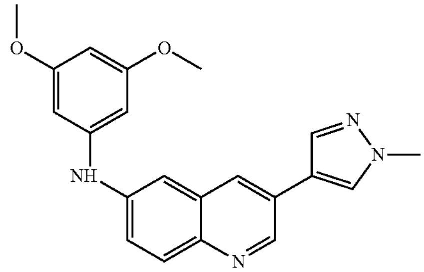


Compound 3



-continued

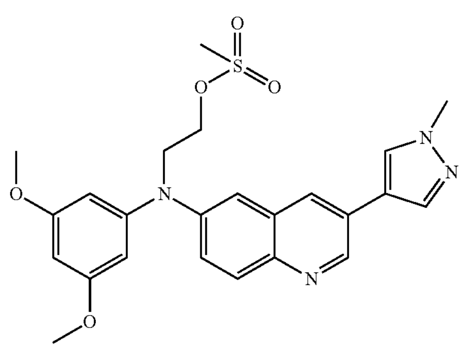
Interm. 7



NaH (179 m g; 4.5 mmol, 60% dispersion in mineral oil) was added portionwise to a solution of intermediate 7 (1 g; 2.8 mmol) in N,N-dimethylformamide (15 ml) at 5° C. under N_2 flow. The reaction mixture was stirred at 5° C. for 1 hour. Then, a solution of (2-bromoethoxy)-tert-butyldimethylsilane (0.77 ml; 3.6 mmol) in DMF (2 ml) was added dropwise at 5° C. under N_2 flow. The reaction mixture was stirred overnight at room temperature. LC/MS showed a conversion of 46%. NaH (125 mg; 3.1 mmol, 60% dispersion in mineral oil) was added portionwise to the solution and (2-bromoethoxy)-tert-butyldimethylsilane (0.6 ml; 2.8 mmol) was added dropwise and the mixture stirred at room temperature for 20 hours. Again NaH (132 mg; 3.3 mmol, 60% dispersion in mineral oil) was added portionwise to the solution and (2-bromoethoxy)-tert-butyldimethylsilane (0.6 ml; 2.8 mmol) was added dropwise and the mixture stirred at room temperature for 6 hours. The reaction was poured out onto ice water and EtOAc was added. The organic layer was separated, washed with K_2CO_3 10%, brine, dried ($MgSO_4$), filtered and the solvent was evaporated to dryness. The residue was purified by chromatography over silica gel (15-40 μm 90 g, mobile phase gradient from 99% DCM, 1% MeOH to 97% DCM, 3% MeOH). to give 0.76 g (53%) of intermediate 9, 0.19 g of fraction 1 and 0.4 g of unreacted intermediate 7.

Fraction 1 was purified by preparative liquid chromatography on (Spherical Silica 5 μm 150×30.0 mm). Mobile phase (Gradient from 100% DCM, 0% MeOH to 93% DCM, 7% MeOH) to afford a residue (95 mg) which was crystallized from CH_3CN to afford 52 mg (5%) of Compound 3. MP=195-196° C.

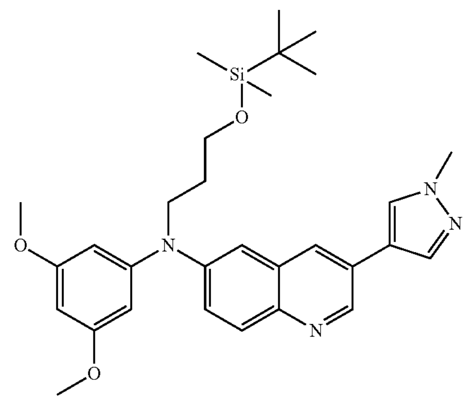
g) Preparation of Intermediate 11



Methanesulfonyl chloride (0.13 ml; 1.7 mmol) was added dropwise to a suspension of Compound 3 (0.34 g; 0.84 mmol), triethylamine (0.3 ml; 1.9 mmol) and 4-dimethylaminopyridine (12 mg; 0.1 mmol) in DCM (7 ml) at 5° C. under N_2. The mixture was stirred at room temperature for 1 hour, and was then poured out onto ice water and DCM was added. The organic layer was decanted, dried over $MgSO_4$, filtered and evaporated to dryness to give 0.58 g of intermediate 11. This compound was used without further purification for the next step.

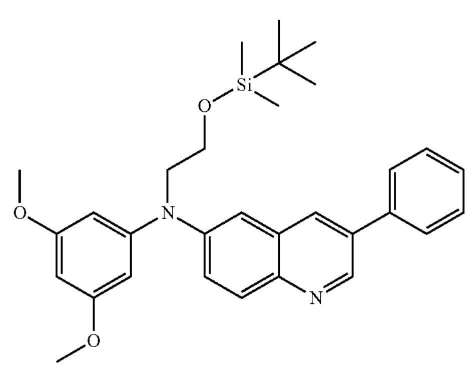
Example A2

Preparation of Intermediate 12



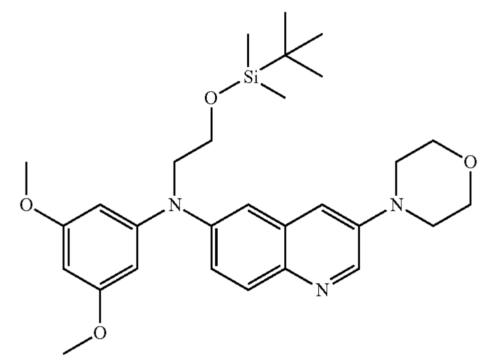
NaH (0.18 g; 4.5 mmol, 60% dispersion in mineral oil) was added portionwise to a solution of intermediate 7 (1 g; 2.8 mmol) in N,N-dimethylformamide (12 ml) at 5° C. under N_2 flow. The reaction mixture was stirred at 5° C. for 1 hour. Then (3-bromopropoxy)-tert-butyldimethylsilane (0.9 ml; 3.6 mmol) was added dropwise at 5° C. under N_2 flow. The reaction mixture was stirred 18 hours at room temperature. The reaction was poured out onto ice water and EtOAc was added. The organic layer was separated, washed with K_2CO_3 10%, brine, dried ($MgSO_4$), filtered and the solvent was evaporated to dryness to give 1.9 g of intermediate 12. This compound was used without further purification for the next step.

Analogous preparation of intermediate 30



starting from intermediate 31 and (2-bromoethoxy)tert-butyldimethylsilane

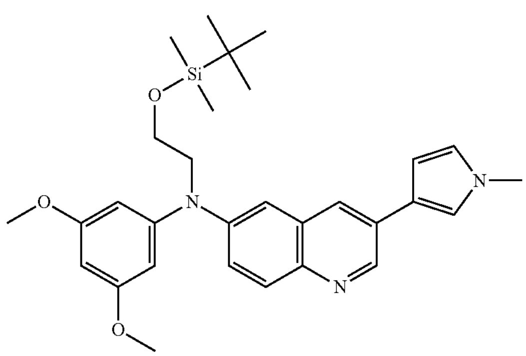
Analogous preparation of intermediate 35



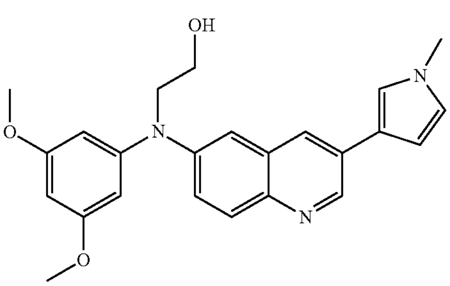
starting from intermediate 36 and (2-bromoethoxy)tert-butyldimethylsilane

Example A2a

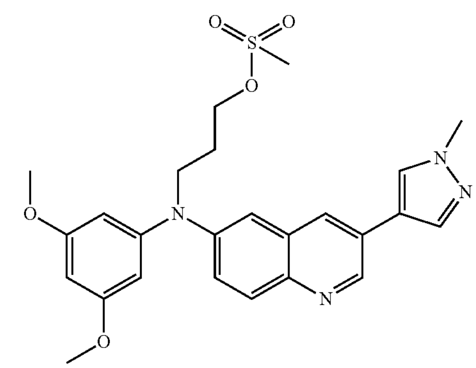
Preparation of Intermediate 45



and compound 61



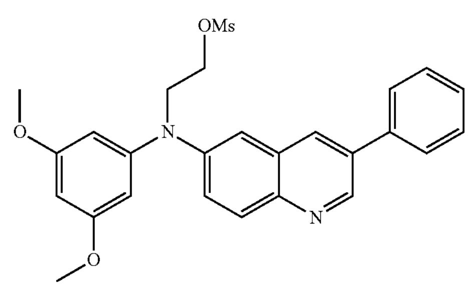
NaH 60% in mineral oil (108.16 mg; 2.70 mmol) was added portion wise to a solution of intermediate 46 (486 mg; 1.35 mmol) in DMF (7 mL) at 5° C. under N_2 flow. The reaction mixture was stirred at 5° C. for 30 minutes and then a solution of (2-bromoethoxy)-tert-butyldimethylsilane (435 μL; 2.03 mmol) in DMF (3 mL) was added drop wise. The reaction mixture was allowed to warm to room temperature and stirred overnight. It was then poured onto ice water and extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, filtered and the solvent was evaporated. The crude product was purified by chromatography over silica gel (irregular SiOH, 15-45 μm, 24 g; mobile phase: gradient from 100% DCM, 0% MeOH to 98% DCM, 2% MeOH). The product fractions were collected and evaporated to dryness yielding 210 mg of intermediate 45 (30%) and 174 mg of an impure fraction of compound 61 which was purified by chromatography over silica gel (irregular SiOH, 15-45 μm, 24 g; mobile phase: gradient from 100% DCM, 0% MeOH to 99% DCM, 1% MeOH). The product fractions were collected and evaporated to dryness yielding 113 mg of the compound which was crystallized from ACN. The precipitate was filtered, washed with ACN, then Et_2O and dried to afford 86 mg of compound 61 (16%). MP: 158° C. (DSC).



Example A3

Preparation of Intermediate 13

Methanesulfonyl chloride (0.37 ml; 4.8 mmol) was added dropwise to a suspension of compound 4 (1 g; 2.4 mmol), triethylamine (0.8 ml; 5.5 mmol) and 4-dimethylaminopyridine (30 mg; 0.2 mmol) in DCM (20 ml) at 5° C. under N_2. The mixture was stirred at room temperature for 1 hour. The reaction mixture was poured out onto ice water and DCM was added. The organic layer was decanted, dried over $MgSO_4$, filtered and evaporated to dryness to give 1.2 g of intermediate 13. This compound was used without further purification for the next step.

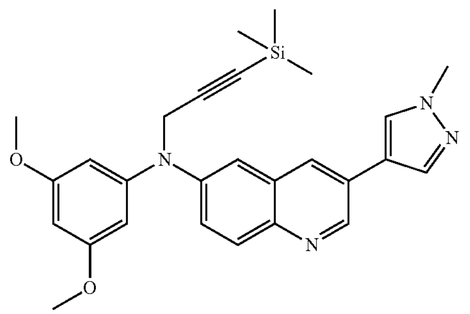


Example A3a

Preparation of Intermediate 34

Methanesulfonyl chloride (0.13 mL; 1.69 mmol) was added dropwise to a solution of compound 50 (260 mg; 0.65 mmol) and triethylamine (0.27 mL; 1.95 mmol) in DCM

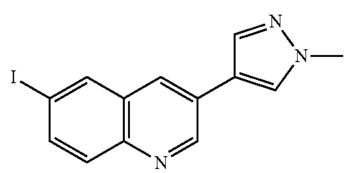
(6.63 mL) at 5° C. under N_2. The solution was stirred at room temperature for 15 hours. The solvent was evaporated to give 300 mg of intermediate 34 (96%) which was used without any purification in the next step.



Example A4

Preparation of Intermediate 14

NaH (1.3 g; 33.3 mmol, 60% dispersion in mineral oil) was added portionwise to a solution of intermediate 7 (6 g; 16.6 mmol) in N,N-dimethylformamide (70 ml) at 5° C. under N_2 flow. The reaction mixture was stirred at 5° C. for 30 minutes then 3-bromo-1-(trimethylsilyl)-1-propyne (5.2 ml; 33.3 mmol) was added dropwise at 5° C. under N_2 flow. The reaction mixture was stirred 2 hours at room temperature. The reaction mixture was quenched with water and extracted with EtOAc. The organic layer was decanted, washed with brine, dried over $MgSO_4$, filtered and evaporated to dryness to afford 8.1 g of intermediate. It was used in the next step without any further purification.

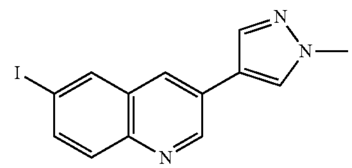


Example A5

Preparation of Intermediate 15

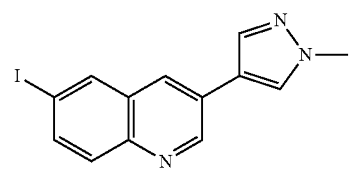
A solution of sodium nitrite (0.17 g, 2.45 mmol) in water (1 ml) was added dropwise to a solution of 3-(1-methyl-1H-pyrazol-4-yl-quinolin-6-yl-amine (0.5 g, 2.2 mmol) in HCl (2.5M in H_2O, 10 ml) at 0° C. The mixture was stirred at 0° C. for 30 minutes. Then, a solution of potassium iodide (0.44 g, 2.7 mmol) in water (1 ml) was added dropwise and the mixture was allowed to rise to room temperature for 3 hours. The reaction mixture was quenched with a solution of sodium hydroxide (3M, 12 ml) until pH 10, and was extracted with a mixture of DCM/MeOH 8/2 (3×100 ml). The organic layers were combined, dried over anhydrous sodium sulfate, filtered and concentrated to dryness. The residue was purified by column chromatography over silica gel (eluent: dichloromethane/methanol 98/2). The product fractions were collected and the solvent was evaporated, yielding 0.17 g (23%) of intermediate 15.

Alternative Preparation of Intermediate 15



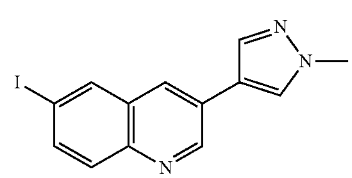
To a solution of NaI (103.5 g; 691 mmol) in ACN (500 ml) were added a solution of 3-(1-methyl-1H-pyrazol-4-yl)-6-quinolinamine (65 g; 290 mmol) in ACN/DMSO (1:1, 220 ml) and 1,1-dimethylethyl ester nitrous acid (44.9 g; 435 mmol). To the above solution was slowly added TFA (2 ml) and heated to 65° C. over 45 minutes and stirred for overnight. The reaction mixture was concentrated under reduce pressure and washed with solution of $NaHSO_3$, water and t-BuOMe, yielding 49.60 g of intermediate 15 (51.0%, purity 90%).

Alternative Preparation of Intermediate 15



To a suspension of 6-bromo-3-(1-methyl-1H-pyrazol-4-yl)-quinoline (intermediate 20) (cas number 1184914-71-3), under argon atmosphere, (0.58 g, 2.0 mmol) in dioxane (10 ml) was added copper iodide (0.038 g, 0.2 mmol), N,N-dimethylethylenediamine (0.043 ml, 0.4 mmol) and sodium iodide (0.603 g, 4 mmol). The reaction mixture was stirred at 120° C. overnight in a sealed tube. The reaction was cooled to room temperature, diluted with EtOAc (15 ml), washed with NH_4OH (33% in H_2O) (10 ml), HCl (aq. 0.1 M) (10 ml) and brine (15 ml). The organic layer was dried (Na_2SO_4) and concentrated to give 0.54 (80%) g of intermediate 15.

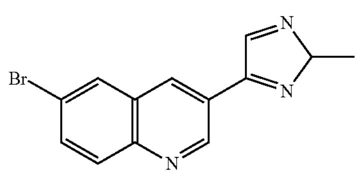
Alternative Preparation of Intermediate 15



A solution of sodium nitrite (7.38 g, 107 mmol) in water (60 ml) was added dropwise at 0° C. to a solution of 3-(1-methyl-1H-pyrazol-4-yl)quinolin-6-yl-amine (24 g, 107 mmol) in aqueous 3 M HCl (10 ml; 428 mmol). The mixture was stirred at 0° C. for 20 minutes and EtOAc (600 mL) was added. Then, a solution of sodium iodide (16 g, 107 mmol) in water (55 ml) was added drop wise at 0° C. The mixture was stirred at 0° C. for 2 hours, at room temperature for 1 hour and then concentrated to dryness. The residue was taken up in a mixture of MeOH (500 mL) and DCM (500 mL) and the resulting mixture was sonicated for 15 minutes. The insolubles were filtered through a pad of Celite® which was rinsed with a mixture of MeOH (300 mL) and DCM (300 mL). Silica gel was added to the filtrate and the mixture was concentrated.

The residue (red brown solid) was purified by chromatography over silica gel (eluent: gradient from DCM/MeOH: 95/5 to 80/20). The fractions containing the product were collected and the solvent was evaporated giving 11.6 g of an intermediate fraction which was taken up in a 10% aqueous solution of $NaHSO_3$ (200 mL). The resulting mixture was extracted with DCM (3×200 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated affording 8.2 g of intermediate 15 (23%).

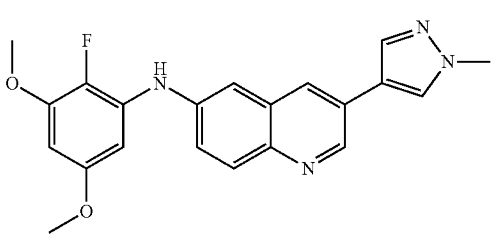
Preparation of Intermediate 20



Under argon atmosphere, sodium nitrite (0.34 g, 4.9 mmol) was added portionwise to a solution of intermediate 5 (0.85 g, 3.8 mmol) in hydrobromic acid (48% in water, 10 ml) over 5 minutes. The mixture was then added to a suspension of copper bromide (0.38 g, 2.7 mmol) in HBr (5 ml) at 65° C. over 5 minutes. The mixture was stirred at 70° C. for 1 h, cooled down to room temperature and diluted with water (20 ml). A solution of sodium hydroxide (3 M, 50 ml) was added until reaching pH=10 and the aqueous layer was extracted with a mixture of dichloromethane/methanol 9/1 (3×250 ml). The organic layers were washed with brine (300 ml), dried over anhydrous sodium sulfate, filtered and concentrated to dryness. The residue was purified by column chromatography over silica gel (mobile phase, 98% DCM, 2% MeOH). The product fractions were collected and the solvent was evaporated to provide 0.82 g of an off-white solid which was further purified by reverse phase chromatography over silica gel (mobile phase; gradient from 60% MeOH, 40% water to 100% MeOH). The product fractions were collected and the solvent was evaporated to provide 0.505 g (46%) of intermediate 20.

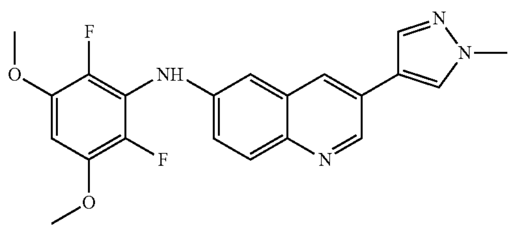
Example A6

a) Preparation of Intermediate 18



A solution of intermediate 15 (5 g; 15 mmol), 2-fluoro-3,5-dimethoxybenzenamine (2.8 g; 16.4 mmol), sodium tert-butoxide (4.3 g; 45 mmol) in dry dioxane (100 ml) was degassed under N_2, then rac-bis(diphenylphosphino)-1,1'-binaphthyl (465 mg; 0.75 mmol) and palladium(II) acetate (47% Pd) (167 mg; 0.75 mmol) were added and the mixture was heated at 100° C. for 15 hours. The reaction mixture was cooled down to room temperature and poured out onto ice water and brine and DCM. The mixture was stirred at room temperature for 30 minutes, then filtered through Celite®. The organic layer was washed with brine then water, was dried over $MgSO_4$, filtered and evaporated to dryness. The crude product was crystallized in DCM, filtered off, the precipitate was washed with Et_2O and dried under vacuum to give 2.9 g of intermediate 18 (51%), MP=118° C.

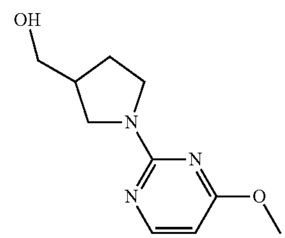
Analogous preparation of intermediate 10



starting from intermediate 15

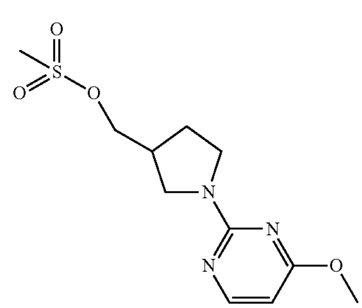
Example A8

a) Preparation of Intermediate 17



A mixture of 2-chloro-4-methoxypyrimidine (2 g; 13.8 mmol), 3-hydroxymethylpyrrolidine (1.68 g; 16.6 mmol) and K_2CO_3 (3.8 g; 27.7 mmol) in acetonitrile (100 ml) was refluxed for 6 hours. The mixture was cooled down, was poured out onto cooled water and extracted with DCM. The organic layer was dried over $MgSO_4$, filtered and evaporated to dryness. The residue was chromatographied over silica gel (15-40 μm 300 g, mobile phase: 0.1% NH_4OH, 97% DCM, 3% MeOH). The product fractions were collected and the solvent was evaporated to give 1.95 g (67%) of intermediate 17.

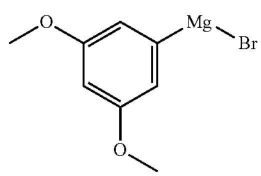
b) Preparation of Intermediate 19



Methanesulfonylchloride (3.6 ml; 46.6 mmol) was added dropwise to a suspension of intermediate 17 (1.95 mg; 9.3 mmol) in DCM (15 ml) and triethylamine (2.4 ml; 16.9 mmol) at 10° C. under N_2. The mixture was stirred at 10° c. for 1 hour, then iced water was added. The mixture was extracted with DCM, dried over $MgSO_4$, filtered and the solvent was evaporated. The resulting residue (3.8 g) was purified by silica gel chromatography (irregular SiO2, 15-40 μm; 40 g; eluent: 99% DCM, 1% MeOH). The product fractions were mixed and the solvent was concentrated to afford 2 g (75%) of intermediate 19.

Example A9

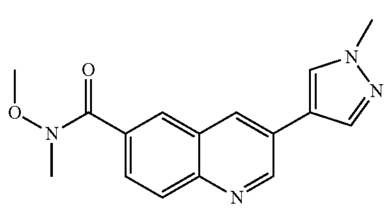
Preparation of Intermediate 21



A catalytic amount of iodine was added to a suspension of magnesium (0.234 g; 9.63 mmol) in THF (1 mL). The mixture was heated with a hot gun until reflux and allowed to cool to room temperature. 1 ml of a solution of 1-bromo-3,5-dimethoxybenzene (2.09 g; 9.63 mmol) in THF (10 mL) was added drop wise and the mixture was heated with a hot gun until reflux and allowed to cool to room temperature. Then, the solution of 1-bromo-3,5-dimethoxybenzene was diluted with THF (5.2 mL) and added drop wise over a period of 20 minutes to the reaction mixture which was refluxed for 1 hour, allowed to cool to room temperature and directly engaged in the next step.

Example A10

Preparation of Intermediate 22

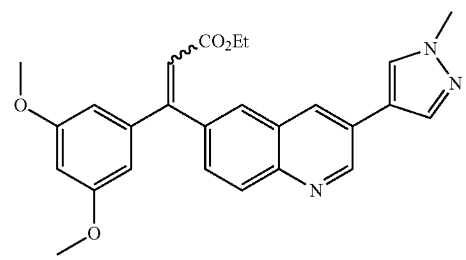


$Pd(Ph_3)_4$ (1.04 g; 0.90 mmol) was added to a solution of intermediate 15 (3.01 g; 8.98 mmol), N,O-dimethylhydroxylamine hydrochloride (1.93 g; 19.8 mmol) and triethylamine (6.51 mL; 46.7 mmol) in toluene (39.3 mL), previously purged with argon. The mixture was then purged with CO and heated at 110° C. for 16 hours under CO atmosphere. The reaction mixture was diluted with a saturated aqueous solution of K_2CO_3 (250 mL) and extracted with DCM/MeOH (95/5; 3×250 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduce pressure.

The brown residue was combined with another crude prepared from 115 mg of intermediate 15. The resulting residue was purified by chromatography over silica gel (eluent: DCM/MeOH:98/2 to 90/10). The product fractions were collected and the solvent was evaporated to afford 2.38 g of intermediate 22 (86%).

Example A11

Preparation of Intermediate 23

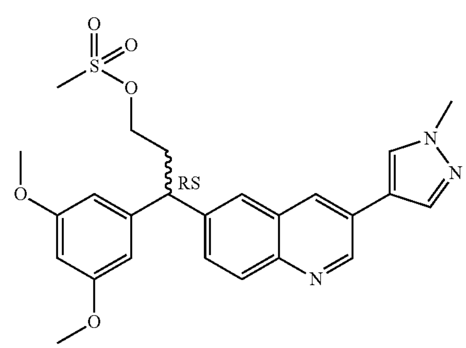


Triethyl phosphonoacetate (1.08 mL; 5.42 mmol) was added drop wise to a suspension of sodium hydride (217 mg; 5.42 mmol) in THF (5 mL) at 0° C. After 1 hour at room temperature, a solution of compound 31 (675 mg; 1.81 mmol) in THF (18.3 mL) was added drop wise and the reaction mixture was heated to reflux for 2 h 30. The reaction mixture was then diluted with water (30 mL) and extracted with DCM (3×30 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduce pressure.

The residue (1.38 g; orange oil) was purified by chromatography over silica gel (eluent: EtOAc/MeOH:99/1). The pure fractions were mixed and the solvent was evaporated to afford 720 mg of intermediate 23 (82%; E/Z or Z/E mixture: 65/35). Intermediate 23 was engaged in the next step without any further purification.

Example A12

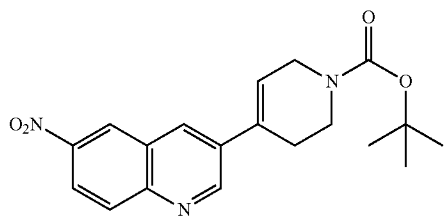
Preparation of Intermediate 24



Methanesulfonyl chloride (0.047 mL; 0.605 mmol) was added dropwise at 0° C. under argon atmosphere to a mixture of compound 34 (0.122 g; 0.302 mmol) and Et_3N (0.105 mL; 0.756 mmol) in DCM (5 mL). The reaction mixture was quenched with ice water (5 mL) and extracted with DCM (3×10 mL). The organic layer was decanted, dried over Na_2SO_4, filtered and evaporated to dryness to give intermediate 24 which was used as such in the next step.

Example A13

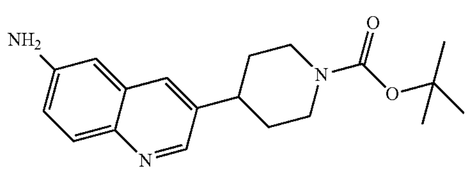
a) Preparation of Intermediate 25



A mixture of 3-bromo-6-nitroquinoline (intermediate1, CAS: 7101-95-3) (13.8 g; 54.5 mmol), (N-tert-butoxycarbonyl)-1,2,3,6-tetrahydropyridine-4-boronic acid pinacol ester (CAS: 286961-14-6) (18.55 g; 59.99 mmol), $Pd(Ph_3)_2Cl_2$ (1.91; 2.73 mmol) and Cs_2CO_3 (35.54 g; 109.07 mmol) was dissolved in dioxane (150 mL) and water (60 mL). The mixture was stirred at 80° C. for 2 h, then poured into water. The precipitate was filtered off. The filtrate was extracted with DCM and concentrated under vacuum.

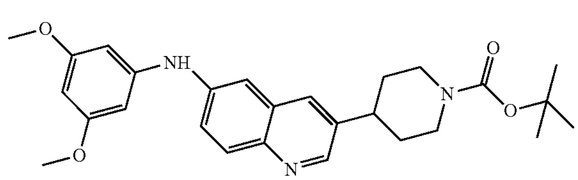
The residue was purified by chromatography over silica gel (gradient eluent: Petroleum Ether/EtOAc: 3/1) yielding 7.5 g of intermediate 25 (97%).

b) Preparation of Intermediate 26



To a solution of intermediate 25 (3 g; 8.44 mmol) in MeOH (250 mL) was added Raney Nickel (0.5 g; 8.44 mmol). The mixture was hydrogenated under pressure (3 bars) at room temperature overnight. The solution was filtered over a pad of Celite® then rinsed with DCM and the solvent was evaporated to give 2.76 g (100%) of intermediate 26, which was used without further purification in the next step.

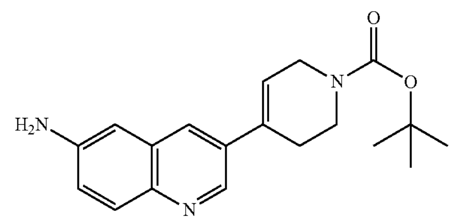
c) Preparation of Intermediate 27



Under N_2, Pd_2 dba_3 (0.632 g; 069 mmol) was added to a previously degassed mixture of intermediate 26 (2.26 g; 6.9 mmol), 1-bromo-3,5-dimethoxybenzene (1.5 g; 6.9 mmol), cesium carbonate (6.75 g; 20.7 mmol) and XPhos (0.329 g; 0.69 mmol) in 2-methyl-2-propanol (98.4 mL). The mixture was heated at 100° C. for 5 hours. The reaction mixture was poured into water, filtered through a pad of Celite® and washed with EtOAc. Water was added to the filtrate and the aqueous layer was extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, filtered and the solvent was evaporated. The residue was purified by chromatography over silica gel (Irregular SiOH, 120 g, 15-40 μm: eluent: DCM/MeOH: 100/0 to 97/3). The pure fractions were collected and the solvent was evaporated to give 2.5 g (78%) of intermediate 27.

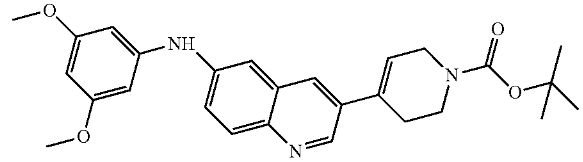
Example A14

a) Preparation of Intermediate 28



In a round bottom flask, intermediate 25(1.9 g; 5.35 mmol) and ammonium chloride (2.86 g; 53.46 mmol) were diluted in THF/MeOH/water (1/1/1) (114 mL). Then, iron (1.49 g; 26.73 mmol) was added and the reaction mixture was refluxed for 4 h. The reaction mixture was filtered over a pad of Celite® and rinsed with DCM. The solvent was evaporated. The aqueous layer was basified with saturated aqueous $NaHCO_3$, then extracted twice with DCM. The organic layer were combined, dried over $MgSO_4$, filtered and concentrated. The residue was purified by chromatography over silica gel (irregular SiOH, 300 g, 15-40 μm; mobile phase: 99% DCM, 1% MeOH). The pure fractions were mixed and the solvent was evaporated to give 1.1 g of intermediate 28. (63%)

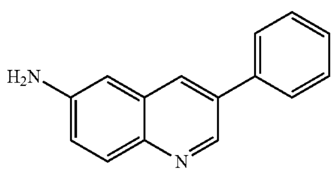
b) Preparation of Intermediate 29



A solution of intermediate 28 (1.1 g; 3.38 mmol), 1-bromo-3,5-dimethoxybenzene (0.734 g; 3.38 mmol), cesium carbonate (3.3 g; 10.14 mmol) and XPhos (161 mg; 0.338 mmol) in 2-methyl-2-propanol (48 mL) was degassed under N_2. Pd_2 dba_3 (310 mg; 0.338 mmol) was added and the mixture was stirred at 100° C. for 5 h. The reaction mixture was poured into water, filtered through a pad of Celite® and washed with EtOAc. Water was added to the filtrate and extracted with AcOEt. The organic layer was washed with brine, dried over $MgSO_4$, filtered and the solvent was evaporated. The residue was purified by chromatography over silica gel (irregular SiOH, 120 g, 15-40 μm, eluent: gradient from DCM/MeOH: 100/0 to 97/3). The pure fractions were mixed and the solvent was evaporated to give 1.37 g of intermediate 29(87%).

Example A15

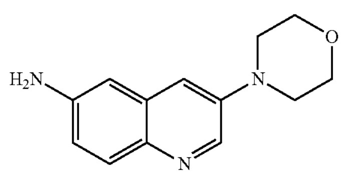
Preparation of Intermediate 32



A solution of intermediate 33 (1.97 g; 7.87 mmol) and Pd on carbon (10 wt %) (0.42 g; 0.393 mmol) in THF (75 ml) and MeOH (75 ml) was stirred under 1 atm of H_2 at room temperature for 3 hours. The reaction mixture was filtered though a pad of Celite® and the solvent was concentrated under vacuum.

The residue was purified by chromatography over silica gel (15-40 μm, 40 g, Mobile phase: gradient from 100% DCM to 98% DCM 2% MeOH). The product fractions were collected and evaporated to dryness to give 1.24 g of intermediate 32 (72%).

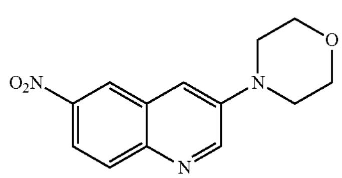
Analogous preparation of intermediate 37



starting from intermediate 38

Example A16

Preparation of Intermediate 38



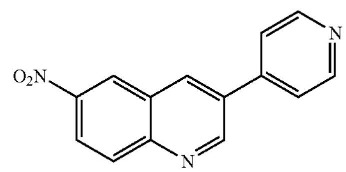
This reaction was carried out by 4 pots on 5 g scale each in parallel.

To a solution of 3-bromo-6-nitroquinoline (intermediate 1), CAS: 7101-95-3) (5 g; 19.76 mmol) in dioxane (100 mL) was added morpholine (2.06 g; 23.7 mmol), Pd_2 dba_3 (904 mg mg; 0.99 mmol), Xantphos (571 mg; 0.99 mmol) and Cs_2CO_3 (12.87 g; 39.5 mmol) under N_2. The mixture was stirred at 110° C. for 25 h under N_2. Then, it was cooled to room temperature and quenched with water. The aqueous mixture was extracted with DCM (3*300 ml) and the combined organic extracts were washed with brine, dried over Na_2SO_4, filtered and the solvent was concentrated under reduced pressure.

The crude product, coming from the 4 reactions, was purified by chromatography over silica gel (Eluent: gradient DCM/EtOAc from 50/1 to 20/1). The desired fractions were collected and evaporated to give 8.25 g of intermediate 38 (41%)

Example A17

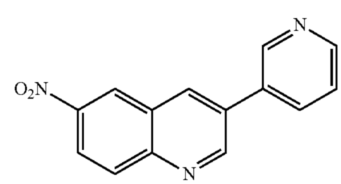
a) Preparation of Intermediate 40



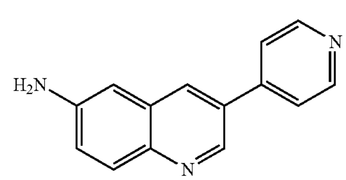
A solution of 3-bromo-6-nitroquinoline (intermediate 1, CAS: 7101-95-3) (3.141 g, 12.41 mmol), pyridine-4-boronic acid pinacol ester (3.055 g, 14.89 mmol), Na_2CO_3 (3.95 g, 37.24 mmol) in dioxane (38.6 ml) and water (15.4 ml) was degassed with argon for 15 min prior to the addition of $PdCl_2$(dppf) (0.454 g, 0.621 mmol) at room temperature. The suspension was stirred under argon at reflux overnight. The reaction mixture was cooled to room temperature. The suspension was filtered through a pad of Celite®, rinsed with a solution of DCM/methanol (8:2) and the filtrate was concentrated under reduced pressure to afford a dark brown solid (7.15 g).

The crude product was adsorbed on silica gel and purified by chromatography over silica gel (eluent: DCM/acetone: 95:5 to 90:10). The product fractions were collected and the solvent was evaporated to afford 1.54 g of intermediate 40 (49%; brown solid).

Analogous preparation of intermediate 44



Reaction performed in MeOH instead of dioxane



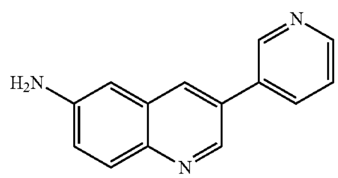
b) Preparation of Intermediate 41

A suspension of intermediate 40 (1.542 g, 6.137 mmol) in THF (15.7 ml) and MeOH (5.7 ml) was purged with argon prior to the addition of a suspension of raney Nickel, 50% slurry in water (0.396 g, 6.751 mmol) in MeOH (10 ml) at room temperature. The brown suspension was purged with argon, purged with hydrogen and stirred under hydrogen (1 atm.) at room temperature overnight. The suspension was filtered through a pad of Celite®, washed with a solution of

DCM/methanol (1:1) and the filtrate was concentrated under reduced pressure to afford a brown orange solid (1.25 g).

The crude product was adsorbed on silica gel and purified chromatography over silica gel (eluent: DCM/methanol 100:0 to 95:5). The product fractions were collected and the solvent was evaporated to afford 400 mg of intermediate 41 (29%; green yellow solid).

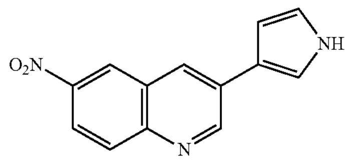
Analogous preparation of intermediate 43



starting from intermediate 44

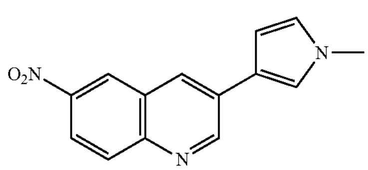
Example A18

a) Preparation of Intermediate 48



A mixture of 3-bromo-6-nitroquinoline (intermediate 1, CAS: 7101-95-3) (7.23 g, 28.62 mmol); 1-(triisopropylsilyl)-1H-pyrrol-3-ylboronic acid pinacol ester (CAS: 365564-11-0) (10 g; 28.62 mmol), $Pd(Ph_3)_2Cl_2$ (0.603 g; 0.86 mmol) and potassium acetate (5.6 g; 57.24 mmol) in DME (100 mL) and water (20 mL) was stirred at 80° C. overnight. The reaction mixture was filtered and concentrated. DCM was added to induce crystallization. The residue was filtered affording 4.5 g of intermediate 48.

b) Preparation of Intermediate 49

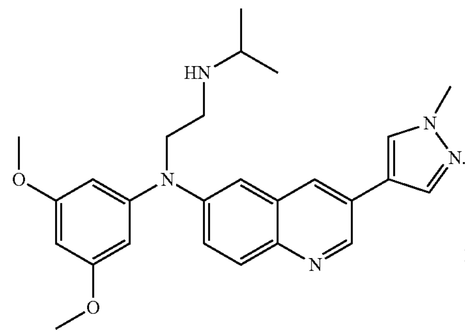


Sodium hydride, 60% in mineral oil (2.2 g; 55 mmol) was added drop wise at 0° C. to a solution of intermediate 48 (4.5 g; 18.81 mmol) in DMF (100 mL). Methyl iodide (8.016 g; 56.47 mmol) was added. The mixture was stirred at room temperature for 2 h. Water was added to induce crystallization. The residue was filtered and washed with cooled water affording 4.82 g intermediate 49.

B. Preparation of the Compounds

Example B1

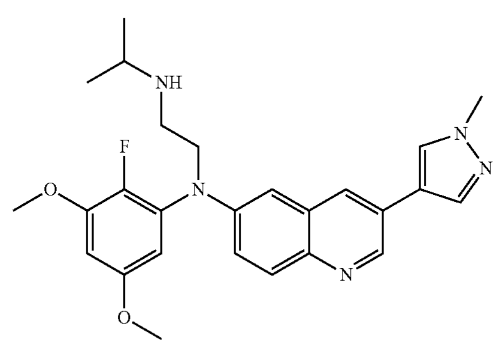
Preparation of Compound 1



1.71 HCl

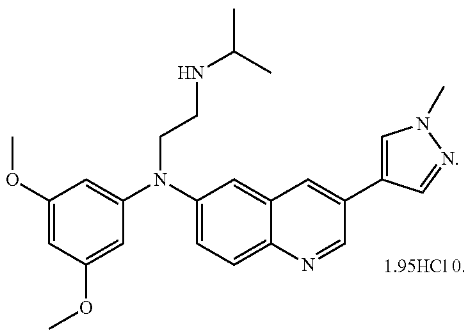
KOH (932 mg; 14.1 mmol) was dissolved in THF (7 ml) and H_2O (distilled, 0.17 ml). Intermediate 7 (341 mg; 0.95 mmol), then tetrabutylammonium bromide (76.5 mg, 0.24 mmol) were added to the mixture and stirred at room temperature for 5 minutes. The reaction mixture was heated at 50° C. for 1 hour. Then N-(2-chloroethyl)-2-propanamine, hydrochloride (225 mg, 1.4 mmol) was added and the reaction mixture was stirred at 50° C. for 18 hours. N-(2-chloroethyl)-2-propanamine, hydrochloride (76 mg, 0.48 mmol) was added and the reaction mixture was stirred at 50° C. for 5 hours. Water was added and the reaction mixture was extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, filtered and evaporated to dryness. The crude product was purified by chromatography over silica gel (5 μm, mobile phase:Gradient from 0.2% NH_4OH, 98% DCM, 2% MeOH to 0.8% NH_4OH, 92% DCM, 8% MeOH). The desired product fraction was collected and the solvent was evaporated. The residue was dissolved in MeOH, 2 drops of HCl (37%) were added and the reaction mixture was stirred at room temperature for 2 minutes. The mixture was evaporated, taken up with CH_3CN and crystallized from CH_3CN to afford 41 mg of compound 1 (9%) as a chlorohydrate.

Analogous preparation of compound 2



starting from intermediate 18

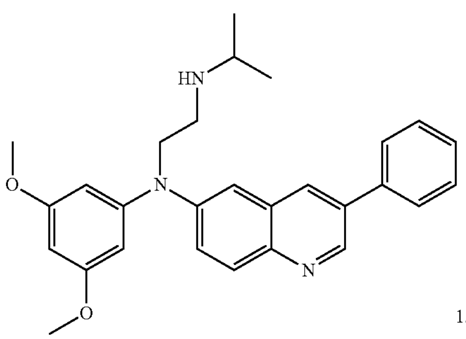
Alternative Preparation of Compound 1



1.95HCl 0.19 H_2O

A mixture of intermediate 11 (0.58 g; 1.2 mmol) in isopropylamine (9 ml; 117 mmol) was heated at 90° C. for 4 hours in sealed tube. The reaction mixture was cooled to room temperature and the mixture was evaporated until dryness. The crude product was purified by chromatography over silica gel (5 μm; mobile phase: gradient from 100% DCM to 0.5% NH_4OH, 95% DCM, 5% MeOH). The pure fractions were collected and the solvent was evaporated to afford 0.17 g (31%). The residue was taken up with CH_3CN/EtOH, 3 drops of HCl 37% were added and the product was crystallized from CH_3CN/EtOH to afford 0.16 g (25%) of compound 1 as a chlorohydrate.

Analogous preparation of compound 51

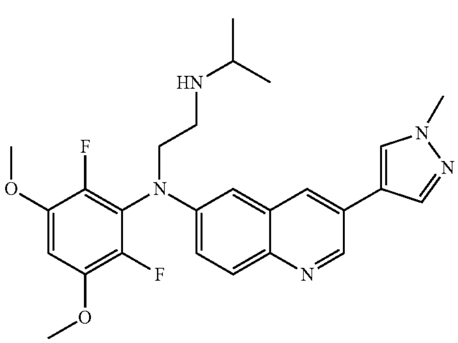


1.88 HCl

starting from intermediate 34

Example B1a

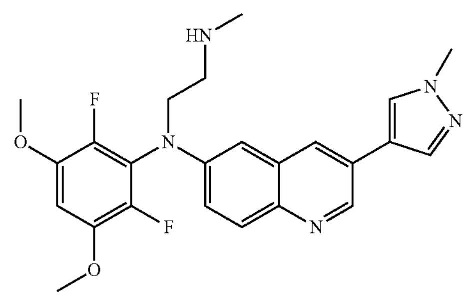
Preparation of Compound 42



Intermediate 10 (500 mg; 1.26 mmol) then tetrabutylammonium bromide (203.3 mg; 0.63 mmol) were added to a solution of KOH (1.25 g; 18.9 mmol) in 2-methyltetrahydrofuran (15 mL) and water (1 mL) at rt. The reaction mixture was heated at 50° C. for 1 h, then 2-isopropylaminoethylchloride hydrochloride (CAS 6306-61-2) (279 mg; 1.77 mmol) was added. The reaction mixture was heated at 50° C. for 20 hours. The reaction mixture was cooled to rt, then poured into water and brine. EtOAc was added and the organic layer was washed with brine, dried over $MgSO_4$, filtered and evaporated to dryness. The residue (0.7 g) was purified by chromatography over silica gel (irregular SiOH, 15-40 μm 30 g; mobile phase: 0.4% NH_4OH, 98% DCM, 2% MeOH). The pure fractions were collected and evaporated to dryness to give 130 mg which was crystallized from Et_2O to give 88 mg (14%) of compound 42. M.P.: 75° C. (gum, Kofler).

Example B1b

Preparation of Compound 43

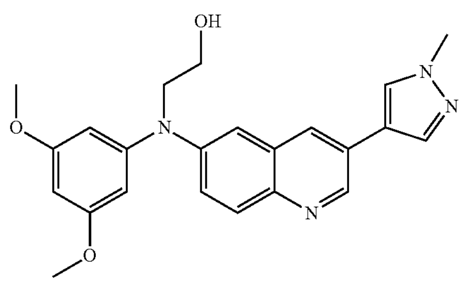


as a HCl salt

Intermediate 10 (0.6 g; 1.51 mmol), then tetrabutylammonium bromide (244 mg; 0.76 mmol) were added to a solution of KOH (1.5 g; 22.7 mmol) in 2-methyltetrahydrofuran (30 mL) and water (1.2 mL) at rt. The reaction mixture was heated at 50° C. for 1 h, then (2-chloroethyl)methylamine (212.4 mg; 2.3 mmol) was added. The reaction mixture was heated at 50° C. for 15 hours. The reaction mixture was cooled to rt, then poured into water and brine. EtOAc was added and the organic layer was washed with brine, dried over $MgSO_4$, filtered and evaporated to dryness. The residue (0.8 g) was purified by chromatography over silica gel (Sperical Silica, 5 μm 150×30.0 mm; mobile phase: gradient from 0.2% NH_4OH, 98% DCM, 2% MeOH to 1.2% NH_4OH, 88% DCM, 12% MeOH). The pure fractions were collected and evaporated to dryness to give 82 mg an intermediate fraction (82 mg) which was solubilized in Et_2O. HCl (3 eq.) was added and the precipitate was filtered off, washed with Et_2O and dried under vacuum to give 71 mg (8%) of compound 43. M.P.: 180° C. (gum, Kofler).

Example B2

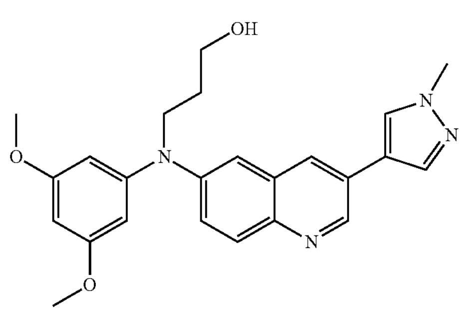
Preparation of Compound 3



A 1M solution of tetrabutylammonium fluoride in THF (4.8 ml; 4.8 mmol) was added dropwise to a solution of intermediate 9 (2 g; 4 mmol) in THF (40 ml) at room temperature. The reaction mixture was stirred at room temperature for 18 hours. The mixture was poured out onto ice water and EtOAc was added. The mixture was basified with K_2CO_3 10% and the organic layer was separated, washed with brine, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue was triturated from diethyl ether, filtered and dried under vacuum, yielding 0.34 g (21%) of compound 3.

Example B3

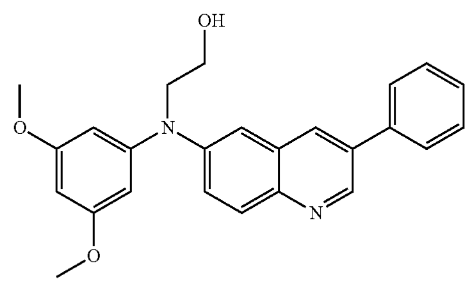
Preparation of Compound 4



A 1M solution of tetrabutylammonium fluoride in THF (3.33 ml; 3.33 mmol) was added dropwise to a solution of intermediate 12 (1.48 g, 2.8 mmol) in THF (50 ml) at room temperature. The reaction mixture was stirred at room temperature for 1 h30. The mixture was poured out onto ice water and EtOAc was added and the mixture was basified with K_2CO_3 10%. The reaction mixture was extracted, the organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue (1.9 g) was purified by chromatography over silica gel (40 g, 15-40 μm, mobile phase 97/3/0.1 DCM/MeOH/NH_4OH) to afford 1.08 g of compound 4.

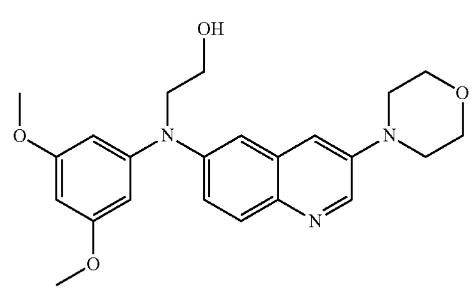
Example B3a

Preparation of Compound 50



Tetrabutylammonium fluoride (1M in THF) (1.17 mL; 1.17 mmol) was added dropwise to a solution of intermediate 30 (600 mg; 1.17 mmol) in THF (25 ml) at 10° C. Then, the reaction mixture was stirred at room temperature for 15 hours and the mixture was poured onto ice water. EtOAc was added and the mixture was basified with 10% aqueous K_2CO_3. The organic layer was separated, washed with brine, dried over $MgSO_4$, filtered and the solvent was evaporated to dryness. The residue (550 mg) was purified was purified by chromatography over silica gel (irregular SiOH, 15-40 μm 30 g; mobile phase: 0.1% NH_4OH, 97% DCM, 3% MeOH, flow rate 20 ml/min). The fractions containing the product were combined and the solvent was evaporated. 2 fractions with different purity of compound 50 were obtained: 200 mg of a fraction A (43%) and 190 mg of a fraction B (41%). The fraction B was partitioned between EtOAc and brine. The organic layer was washed twice with brine, dried over $MgSO_4$, filtered and the solvent was evaporated to dryness to give an intermediate fraction which was taken up with Et_2O. The precipitate was filtered and dried under vacuum to give 56 mg of compound 50 (12%). MP: 111° C. (DSC)

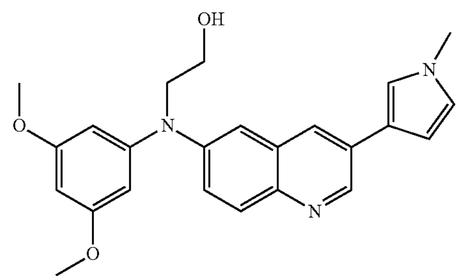
Analogous preparation of compound 54



starting from intermediate 35

Example B3b

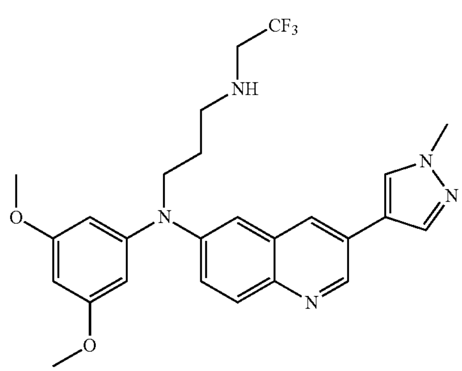
Preparation of Compound 61



TBAF (1M in THF) (4.06 mL; 4.06 mmol) was added drop wise to a solution of intermediate 45 (210 mg; 0.41 mmol) in THF (3.5 mL) at 5° C. under N_2 flow. The reaction mixture was stirred at room temperature for 6 hours, then poured onto 10% aqueous K_2CO_3 and extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, filtered and the solvent was evaporated. The crude product was purified by chromatography over silica gel (irregular SiOH, 15-45 μm 24 g; mobile phase: gradient from 100% DCM, 0% MeOH to 99% DCM, 1% MeOH). The product fractions were collected and evaporated to dryness to give 113 mg of a compound which was crystallized from ACN. The precipitate was filtered, washed with ACN, then Et_2O and dried yielding 93 mg of compound 61 (57%). MP: 158° C. (DSC).

Example B4

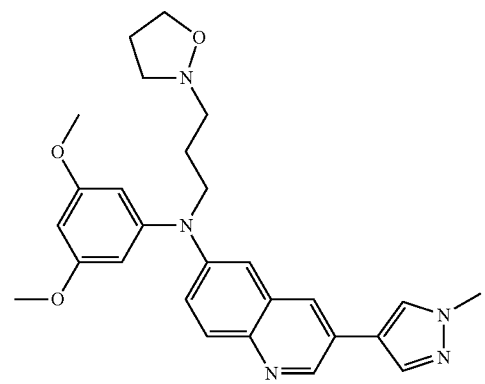
Preparation of Compound 5



(1.78HCl $0.88H_2O$ $0.17C_6H_{14}O0.1C_2H_6O$)

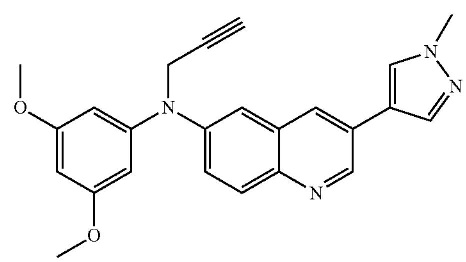
A mixture of intermediate 13 (1.4 g; 2.8 mmol) in 2,2,2-trifluoroethylamine (10 ml) was heated at 90° C. for 4 hours in sealed tube. The reaction mixture was cooled to room temperature and the mixture was evaporated until dryness. The crude product was purified by chromatography over silica gel (Spherical silica, 5 μm, 300 g; mobile phase 0.1% NH_4OH, 98% DCM, 2% MeOH). The product fractions were collected and the solvent was evaporated. The residue (0.6 g) was purified by achiral SFC on (AMINO 6 μm 150×21.2 mm, mobile phase (0.3% isopropylamine, 75% CO_2, 25% MeOH)). The product fractions were collected and the solvent was evaporated. The residue (0.4 g) was dissolved in MeOH then 3 drops of HCl were added. The mixture was evaporated and crystallized from ACN and washed with DIPE to afford 0.34 g of compound 5 (20%)

Analogous preparation of compound 19



Example B5

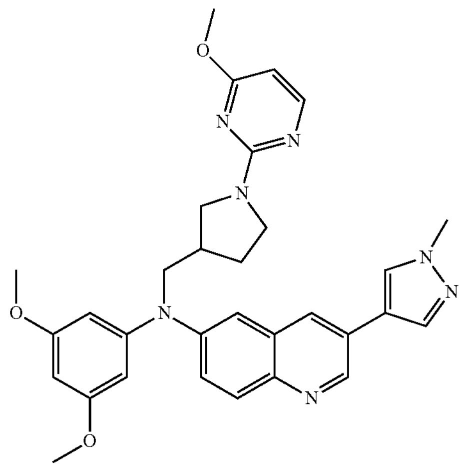
Preparation of Compound 6



A mixture of intermediate 14 (8.1 g; 17.2 mmol) and K_2CO_3 (4.6 g; 34.4 mmol) in MeOH (150 ml) was stirred at room temperature for 2 hours. The reaction mixture was washed with water and extracted with CH_2Cl_2. Then the organic layer was dried ($MgSO_4$), filtered and the solvent was evaporated. The crude product was purified by chromatography over silica gel (40 g, mobile phase 98/2 CH_2Cl_2/MeOH). The pure fractions were collected and the solvent was evaporated to afford 5.5 g (80%) of compound 6.

Example B6

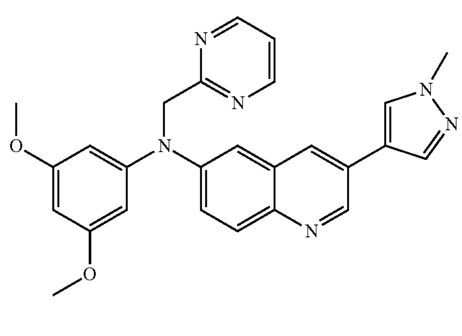
Preparation of Compound 7



Under N_2, NaH (64 mg; 1.6 mmol, 60% dispersion in mineral oil) was added portionwise to a solution of intermediate 7 (0.3 g; 0.84 mmol) in DMF (30 ml) at 5° C. The solution was stirred 30 minutes at 10° C. A solution of intermediate 19 (0.35 g; 1.22 mmol) in DMF (10 ml) was added dropwise. The mixture was heated at 60° C. overnight. The solution was poured out into cooled water, the product was extracted with EtOAc, the organic layer was dried over $MgSO_4$, filtered and evaporated to dryness. The residue was purified by chromatography over silica gel (5 μm, mobile phase gGradient from 70% Heptane, 2% MeOH, 28% EtOAc to 20% MeOH, 80% EtOAc). The desired fractions were collected and the product was crystallized from Et_2O, yielding 100 mg (22%) of compound 7 (MP: 132° C. (DSC)).

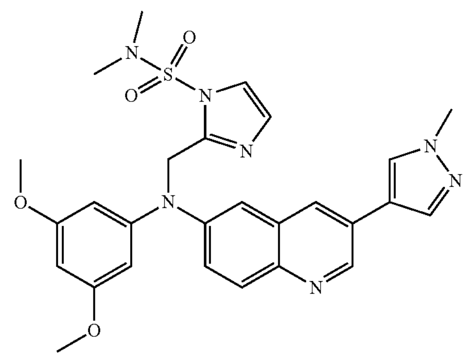
Example B7

Preparation of Compound 8



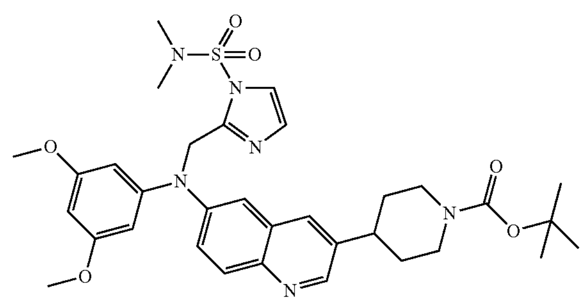
Under N_2 flow, NaH (0.05 g; 1.25 mmol, 60% dispersion in mineral oil) was added to a solution of intermediate 7 (0.3 g; 0.8 mmol) in N,N-dimethylformamide (12 ml) at 0° C. The suspension was stirred 1 hour at 0° C. and 2-(chloromethyl)pyrimidine (0.14 g, 1.0 mmol) was added. The reaction was stirred for 24 hours at room temperature. The mixture was poured into ice-water and EtOAc was added. The organic layer was separated, dried over $MgSO_4$, filtered and the filtrate was evaporated until dryness. The residue (0.84 g) was purified by chromatography over silica gel (5 μm; mobile phase gradient from 70% Heptane, 2% MeOH, 28% EtOAc to 20% MeOH, 80% EtOAc). The pure fractions were collected and the solvent was evaporated. The residue (0.12 g) was crystallized from Et_2O. The precipitate was filtered off and dried to afford 0.087 g (23%) of compound 8. (MP: 151° C. (DSC))

Analogous preparation of compound 9



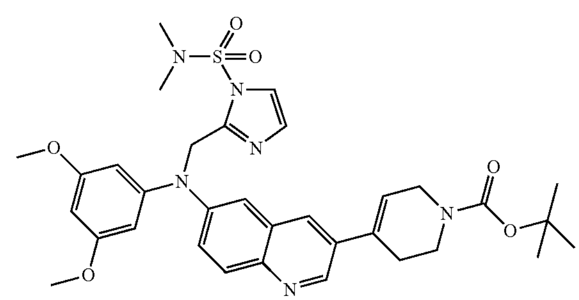
using 2-(chloromethyl)-N,N-dimethyl-1H-Imidazole-1-sulfonamide

Analogous preparation of compound 49



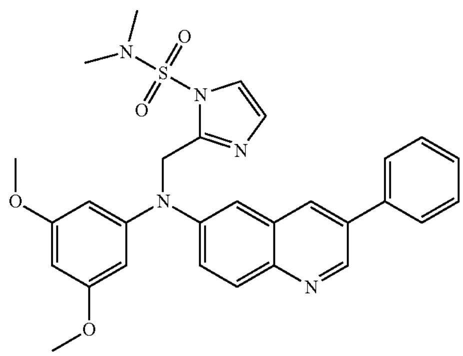
starting from intermediate 27 using 2-(chloromethyl)-N,N-dimethyl-1H-imidazole-1-sulfonamide

Analogous preparation of compound 45



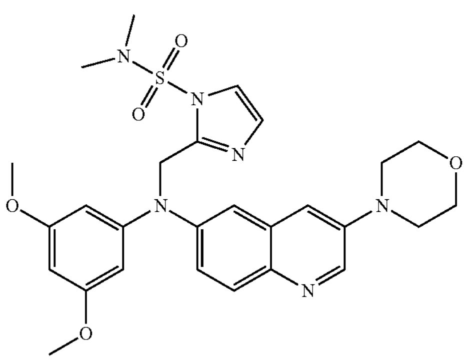
starting from intermediate 29 using 2-(chloromethyl)-N,N-dimethyl-1H-imidazole-1-sulfonamide

Analogous preparation of compound 53



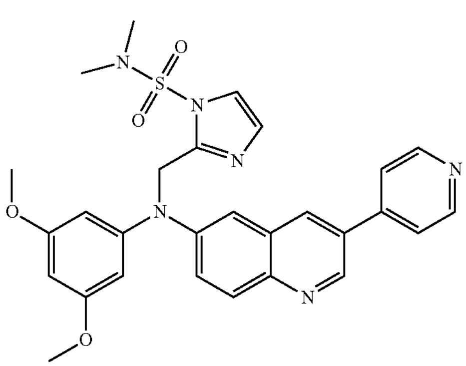
starting from intermediate 31 using 2-(chloromethyl)-N,N-dimethyl-1H-imidazole-1-sulfonamide

Analogous preparation of compound 56



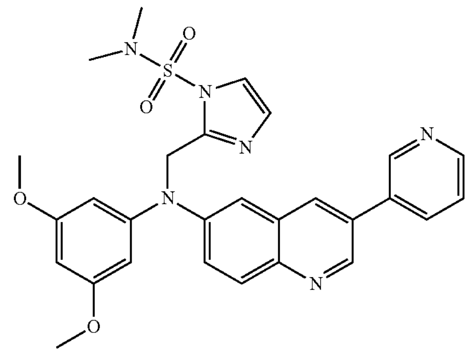
starting from intermediate 36 using 2-(chloromethyl)-N,N-dimethyl-1H-imidazole-1-sulfonamide

Analogous preparation of compound 58



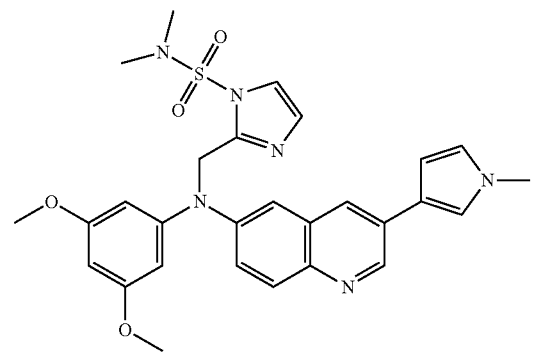
starting from intermediate 39 and 2-(chloromethyl)-N,N-dimethyl-1H-imidazole-1-sulfonamide

Analogous preparation of compound 60



starting from intermediate 42 and 2-(chloromethyl)-N,N-dimethyl-1H-imidazole-1-sulfonamide

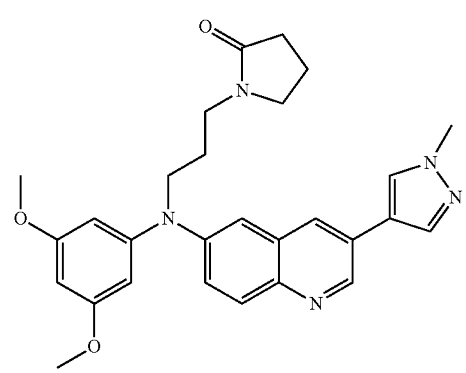
Analogous preparation of compound 63



starting from intermediate 46 and 2-(chloromethyl)-N,N-dimethyl-1H-imidazole-1-sulfonamide

Example B8

Preparation of Compound 10

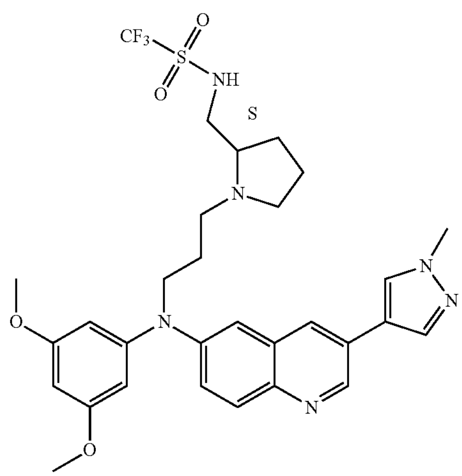


(2.17HCl 1.09H_2O)

NaH (0.3 g; 7.2 mmol, 60% dispersion in mineral oil) was added portionwise to a solution of 2-pyrrolidinone (0.56 ml; 7.2 mmol) in N,N-dimethylformamide (25 ml) at 5° C. under N_2 flow. The reaction mixture was stirred at 5° C. for 1 hour. Then a solution of intermediate 13 (1.2 g, 2.4 mmol) in

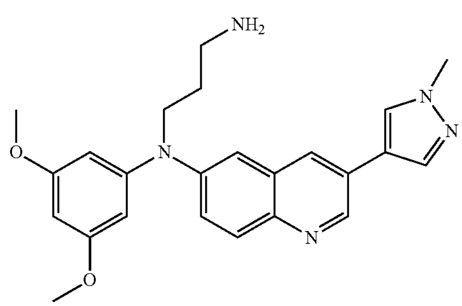
N,N-dimethylformamide (15 ml) was added dropwise at 5° C. The reaction mixture was stirred overnight at room temperature. The reaction mixture was poured out onto ice water and EtOAc was added. The organic layer was separated, washed with brine, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue (1.1 g) was purified by chromatography over silica gel (15-40 μm 300 g; mobile phase 40% Heptane, 10% MeOH, 50% EtOAc). The pure fractions were collected and the solvent was evaporated. The residue (0.35 g) was dissolved in MeOH and 3 eq. of HCl 5N were added. The precipitate was filtered and dried to afford 0.35 g (28%) of compound 10 (MP: 142° C. (Kofler)).

Analogous preparation of compound 47 starting from intermediate 13 and 1,1-trifluoro-N-[(2S)-2-pyrrolidinylmethyl]methanesulfonamide



Example B9

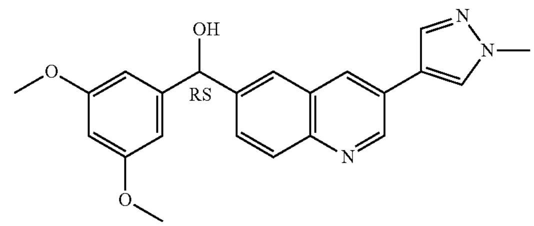
Preparation of compound 11



Intermediate 7 (0.22 g; 0.61 mmol) was added to a solution of potassium hydroxide (0.6 g; 9.2 mmol), tetrabutylammonium bromide (0.078 g; 0.25 mmol) in dry THF (3 ml) and water (0.05 ml). The reaction mixture was stirred at 50° C. for 30 minutes then 3-bromopropylamine hydrochloride (0.34 g; 1.6 mmol) was added portionwise and stirred at 50° C. for 48 hours. The reaction mixture was cooled to room temperature. The reaction was poured out onto ice water and EtOAc was added. The organic layer was separated, washed with brine, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue (0.22 g) was purified by chromatography over silica gel (5 μm; mobile phase gradient from 0.2% NH_4OH, 98% DCM, 2% MeOH to 1.3% NH_4OH, 87% DCM, 13% MeOH). The pure fractions were collected and concentrated to give 0.068 g (27%) of compound 11.

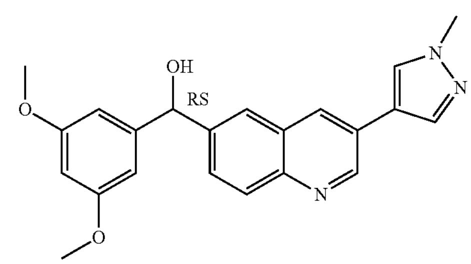
Example B10

Preparation of Compound 12

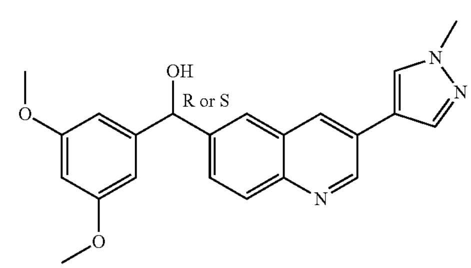


The reaction was performed in anhydrous conditions under argon atmosphere. Chloro(1-methylethyl)-magnesium (2M in THF, 0.18 ml, 0.36 mmol) was added to a solution of intermediate 15 (0.1 g, 0.3 mmol) in THF (1 ml) at 0° C. The reaction mixture was stirred at 0° C. for 1 hour. Then, a solution of 3,5-dimethoxybenzaldehyde (0.06 g, 0.36 mmol) in THF (0.50 ml) was added dropwise at 0° C. The reaction mixture was stirred at 0° C. for 1 hour. The reaction mixture was quenched with a saturated solution of ammonium chloride (3 ml) and was extracted with dichloromethane (3×5 ml). The organic layers were dried over anhydrous sodium sulphate, filtered and concentrated to dryness. The residue was purified by column chromatography over silica gel (mobile phase: 98% DCM, 2% MeOH) The product fractions were collected and the solvent was evaporated, yielding 0.053 g (47%) of compound 12 (MP:184-193° C.).

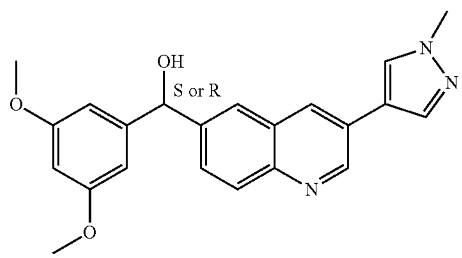
Preparation of Compound 12



Preparation of Compound 38



Preparation of Compound 37



Compound 12 was also prepared as follows:

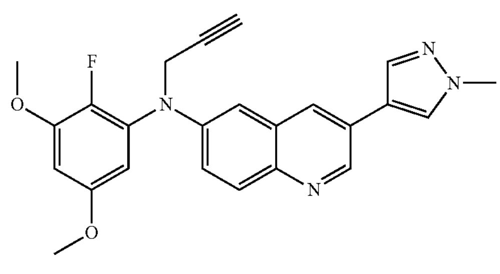
Under N_2 at 10° C., sodium borohydride (60.8 mg; 1.61 mmol) was added to a solution of compound 31 (300 mg; 0.8 mmol) in MeOH (15 mL). The solution was stirred at 10° C. for 45 minutes then, poured onto cooled water. The product was extracted with DCM (twice). A saturated aqueous solution of NaCl was added to the aqueous layer which was then extracted with DCM (twice). The organic layers were combined, dried over $MgSO_4$, filtered and evaporated to dryness.

The residue (300 mg) was purified by chromatography over silica gel (Irregular SiOH, 20-45 μm, 24 g; Mobile phase: 0.1% NH_4OH, 97% DCM, 3% MeOH, flow rate: 25 ml/min). The fractions containing product were mixed and the solvent was evaporated to dryness affording 204 mg of an intermediate fraction which was taken up with Et_2O. The precipitate was filtered and washed with Et_2O to give 126 mg of compound 12 (41%). MP: 240° C. (Mettler-Toledo).

106 mg of compound 12 were purified by chiral SFC (stationary phase: CHIRALCEL OJ-H 5 μm 250×20 mm; mobile phase: 60% CO_2, 40% MeOH). The product fractions were collected and evaporated to dryness yielding 44 mg of compound 37 (16%), 174° C. (Kofler) and 45 mg of compound 38 (16%), 174° C. (Kofler).

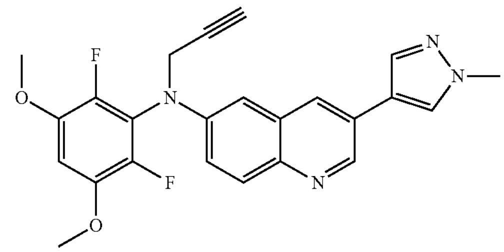
Example B11

Preparation of Compound 15



NaH (79 mg; 2.0 mmol, 60% dispersion in mineral oil) was added portionwise to a solution of intermediate 18 (500 mg; 1.3 mmol) in N,N-dimethylformamide (10 ml) at 5° C. under N_2 flow. The reaction mixture was stirred at 5° C. for 30 minutes then 3-bromo-1-(trimethylsilyl)-1-propyne (0.31 ml; 2.0 mmol) was added at 5° C. under N_2 flow. The reaction mixture was stirred for 15 hours at room temperature. The reaction mixture was quenched with water and EtOAc was added. The organic layer was decanted, washed with brine, dried over $MgSO_4$, filtered and evaporated to dryness. The crude product was crystallized from Et_2O, yielding 320 mg of compound 15 (58%, MP:120° C.).

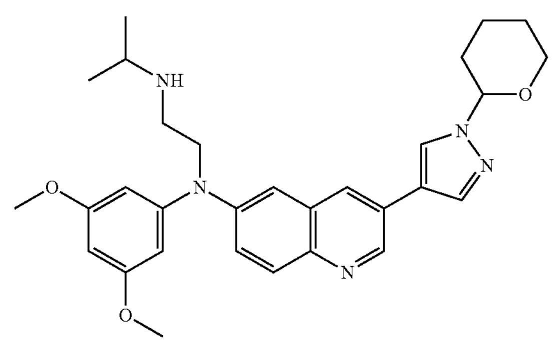
Analogous preparation of compound 20



Starting from Intermediate 10

Example B12

Preparation of Compound 22

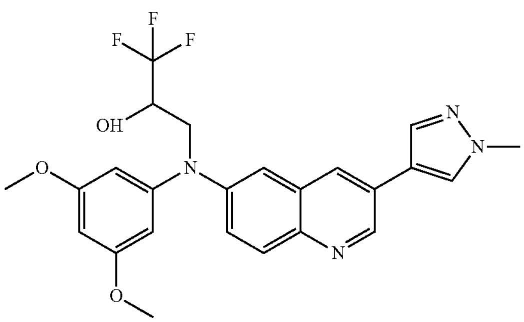


The reaction was performed in anhydrous conditions under argon atmosphere. A solution of intermediate 8 (2.6 g, 6.1 mmol) in DMF (21 ml) was stirred at 0° C. for 15 minutes. Then NaH (1.46 g, 36.6 mmol, 60% dispersion in mineral oil) was added and the reaction mixture was stirred at 0° C. for 15 minutes. Then, 2-propanamine, N-(2-chloroethyl)-, hydrochloride (5.3 g, 33.6 mmol) was added portionwise at 0° C. The brown suspension was stirred at room temperature overnight. The reaction mixture was cooled to 0° C. A saturated solution of ammonium chloride (30 ml) was added and the aqueous layer was extracted with ethyl acetate (2×30 ml). The organic layer was washed with brine (3×40 ml), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by chromatography over silica gel (mobile phase; phase gradient from 90% DCM, 10% acetone to 90% DCM, 10% acetone followed by another gradient from 95% DCM, 5% MeOH to 90% DCM, 10% MeOH). The products fractions were collected and the solvents were evaporated, yielding 2.955 g of compound 22 (94%).

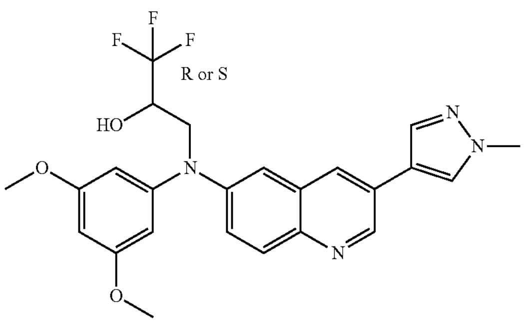
Example B13

Preparation of

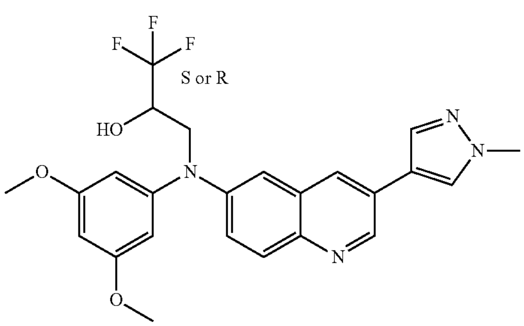
compound 23



compound 24



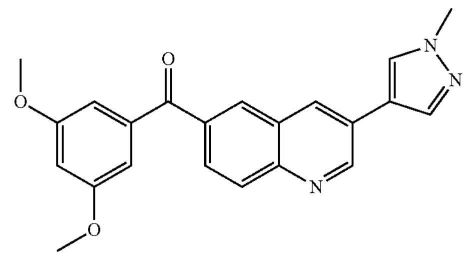
compound 25



NaH (240 mg, 6.1 mmol) was added portionwise to a solution of intermediate 7 (1.1 g, 3.05 mmol) in DMF (12 ml) at 5° C. under N_2 flow. The reaction mixture was stirred at 5° C. for 1 hour then 1,2-epoxy-3,3,3-trifluoropropane (0.32 ml, 3.6 mmol) was added dropwise at 5° C. under N_2 flow. The reaction mixture was stirred for 1 hour at 5° C. then allowed to reach room temperature. The reaction was stirred at room temperature for 1 hour. The reaction was poured out onto ice water and EtOAc was added. The organic layer was separated, washed with brine, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue (1.7 g) was purified by chromatography over silica gel (15-40 μm 300 g, mobile phase 0.1% NH_4OH, 98% DCM, 2% MeOH). The pure fractions were collected and the solvent was evaporated to afford 450 mg of compound 23. The enantiomers were separated by by chiral SFC on). (mobile phase; gradient from 65% CO_2, 35% EtOH to 50% CO_2, 50% EtOH). The pure fractions were collected and the solvent was evaporated, yielding 185 mg of fraction 1 and 170 mg of fraction 2. Fraction 1 was crystallized from DIPE, the precipitate was filtered off and dried to give 126 mg (9%, MP:116° C. (Kofler); $[\alpha]_D$=+120.3° (c=0.39, DMF, 20° C.) of compound 24 Fraction 2 was crystallized from DIPE, the precipitate was filtered off and dried to give 120 mg (8%, MP:118° C. (Kofler), $[\alpha]_D$=−122.6° (c=0.34, DMF, 20° C.) of compound 25

Example B14

Preparation of Compound 31



Intermediate 21 (16.2 mL; 9.64 mmol, 0.59 M in THF) (CAS: 322640-05-1) was added drop wise to a solution of intermediate 22 (2.38 g; 8.03 mmol) in THF (40 mL) at 0° C. The mixture was heated at 50° C. for 3 days, then, poured onto a saturated aqueous NH_4Cl solution (50 mL) and extracted with EtOAc (3×50 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduce pressure. The resulting residue was purified by chromatography over silica gel (eluent: DCM/MeOH:98/2 to 90/10). The product fractions were mixed and the solvent was evaporated yielding 2.01 g of an intermediate fraction (pale orange solid) which was again purified by chromatography over silica gel (eluent: gradient from DCM/MeOH: 95/5 to 90/10). The fractions were collected and the solvent evaporated affording 2 fractions:

Fraction A: 987 mg of compound 31

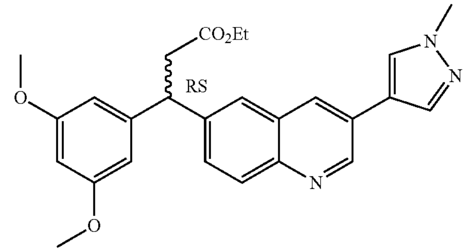
Fraction δ 880 mg of compound 31

Fraction B was purified by reverse phase chromatography (eluent: DCM). The fraction containing the product were mixed and the solvent evaporated giving additional 570 mg of compound 31.

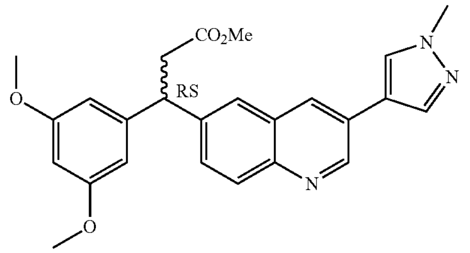
In total, 1.56 g (52%) of compound 31 were obtained. MP: 190° C. (Kofler)

Example B15

Preparation of a mixture of compound 32 and



compound 33

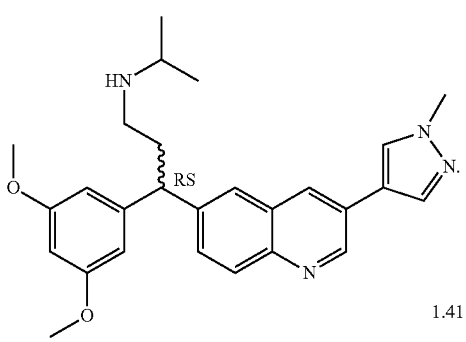


Magnesium (433 mg; 17.8 mmol) was added portion wise to a solution of intermediate 23 (660 mg; 1.62 mmol) in a mixture of MeOH (15 mL) and THF (2 mL) at room temperature and the reaction mixture was stirred for 2 hours at this temperature. Additional magnesium (433 mg; 17.8 mmol) was added and the reaction mixture was stirred for another 3 hours. The reaction mixture was quenched with an aqueous saturated solution NH_4Cl (100 mL). Water (50 mL) was added and the mixture was extracted with DCM (3×50 mL). The organic layers were combined, dried over Na_2SO_4, filtered and concentrated to dryness.

The residue (713 mg; orange gum) was purified by chromatography over silica gel (eluent: DCM/EtOAc: 3/7). The pure fractions were mixed and the solvent was evaporated to afford 385 mg of a mixture of compound 32 and 33, which were engaged in the next step without any further purification.

Example B16

Preparation of Compound 41

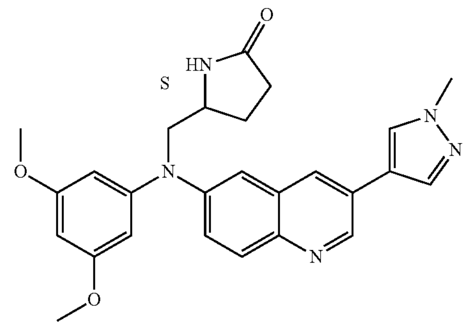


1.41 HCl

A mixture of intermediate 24 (0.145 g; 0.302 mmol) and isopropylamine (3 mL; 35.2 mmol) in 1,4-dioxane (2 mL) was stirred at 90° C. for 16 hours in a sealed tube under argon atmosphere. The reaction mixture was evaporated to dryness. The residue (293 mg) was purified by chromatography over silica gel (irregular SiOH, 15-40 μm; mobile phase: 0.5% NH_4OH, 5% MeOH, 95% DCM). The product fractions were collected and evaporated to dryness. The free base (0.108 g; 80%) was dissolved in MeOH and a solution of HCl 1.25M in iPrOH (1 mL) followed by Et_2O (10 mL) were added. The reaction mixture was evaporated to dryness and dried under vacuum to give 0.084 g (56%) of compound 41 as a hydrochloride. M.P.: >300° C. (DSC)

Example B17

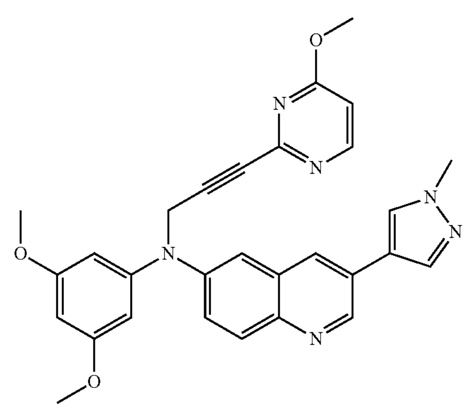
Preparation of Compound 44



Under N_2, NaH (55.5 mg; 1.39 mmol) was added to a solution of intermediate 7 (250 mg; 0.69 mmol) in DMF (10 mL) at 0° C. Then, the suspension was stirred for 1 h at 0° C. and (S)-(+)-5-(Hydroxymethyl)-2-pyrrolidinone p-toluenesulfonate (CAS 51693-17-5) (187 mg; 0.69 mmol) was added. The reaction mixture was stirred overnight at rt. Additional (S)-(+)-5-(Hydroxymethyl)-2-pyrrolidinone p-toluenesulfonate (CAS 51693-17-5) (94 mg; 0.35 mmol) was added. The reaction mixture was stirred at rt 2 days. The solution was poured into cooled water and the product was extracted with EtOAc. The organic layer was dried over $MgSO_4$, filtered and evaporated to dryness. The residue was purified by column chromatography over silica gel (Irregular SiOH, 20-45 μm, 30 g; mobile phase: 0.1% NH_4OH, 97% DCM, 3% MeOH). The fractions containing the product were collected and the solvent was evaporated to dryness. The residue (130 mg) was taken up with Et_2O. The precipitate was filtered and dried under vacuum. The resulting solid (35 mg) was purified by chromatography over silica gel (5 μm, 150×30.0 mm; mobile phase: gradient from 50% Heptane, 3% MeOH, 27% EtOAc to 0% Heptane, 25% MeOH, 75% EtOAc). The pure fractions were collected and evaporated to give 24 mg (8%) of compound 44. MP: gum at 102° C. (Kofler).

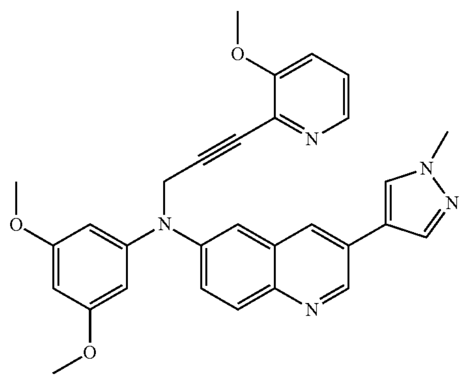
C. Conversions of the Compounds

Conversion C1
Preparation of Compound 16



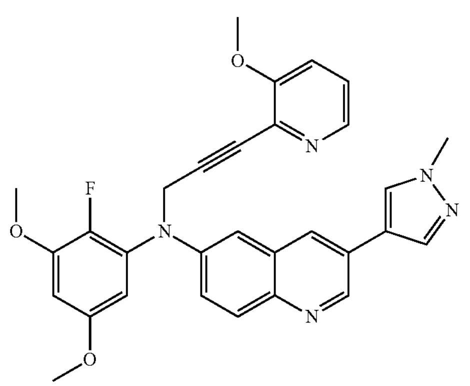
A suspension of compound 6 (0.85 g; 2.2 mmol), 2-chloro-4-methoxypyrimidine (0.22 g; 1.5 mmol) and Et_3N (2.5 mL; 18.3 mmol) in DMSO (18 ml) was degassed under N_2 flow. Dichlorobis(triphenylphosphine)-palladium (0.2 g; 0.3 mmol) and copper(I) iodide (29 mg; 0.15 mmol) were added and the reaction mixture was stirred at 60° C. for 40 minutes. The reaction mixture was cooled down to room temperature, poured out onto water and EtOAc was added. The mixture was filtered off on a pad of Celite®. The organic layer was separated, washed with brine, dried ($MgSO_4$), filtered and evaporated to dryness. The residue (1.4 g) was purified by chromatography over silica gel (20-40 µm, 300 g; mobile phase, 98% DCM, 2% MeOH). The pure fractions were collected and evaporated to dryness. The residue (0.4 g) was crystallized from CH_3CN/MeOH/Et_2O, the precipitate was filtered and dried to give 0.24 g (31%) of compound 16 (MP: 203° C. (DSC)).

Analogous preparation of compound 17



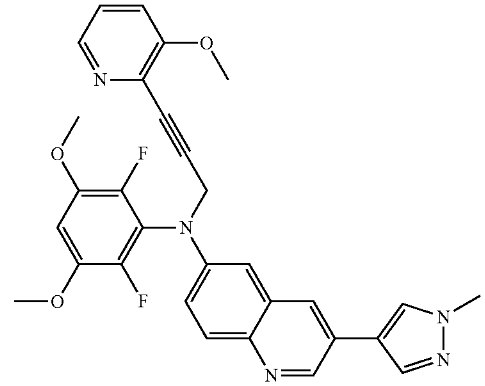
starting from compound 6 using 2-bromo-3-methoxypyridine

Analogous preparation of compound 26



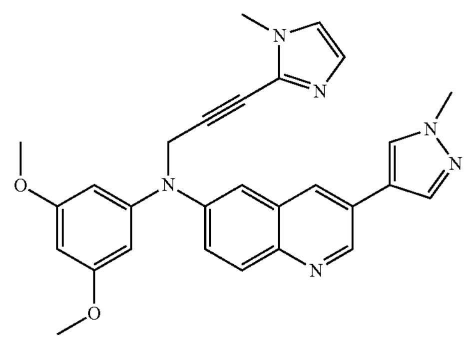
starting from compound 15 using 2-bromo-3-methoxypyridine

Analogous preparation of compound 27



starting from compound 20 using 2-bromo-3-methoxypyridine

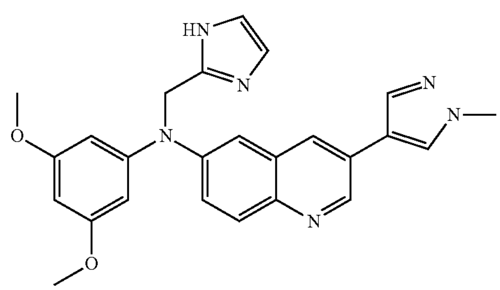
Analogous preparation of compound 48



starting from compound 6 using 2-iodo-1-methyl-1H-imidazole

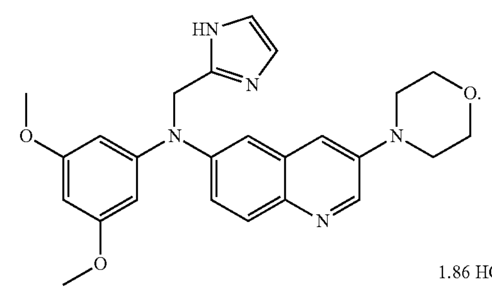
Conversion C2

Preparation of Compound 18



HCl (4M in dioxane; 2.2 ml; 8.7 mmol) was added to a solution of compound 9 (480 mg; 0.87 mmol) in ACN (20 ml) and the reaction mixture was heated at 50° C. for 15 hours. The mixture was poured out onto ice, basified with K_2CO_3 and extracted with DCM. The organic layer was dried over $MgSO_4$, filtered and evaporated till dryness. The obtained residue was purified by chromatography over silica gel (5 µm; mobile phase, gradient from 0.2% NH_4OH, 98% DCM, 2% MeOH to 1% NH_4OH, 89% DCM, 10% MeOH). The pure fractions were collected and the solvent was evaporated. The residue (160 mg) was taken up in Et_2O, filtered and dried, yielding 103 mg of compound 18 (27%; MP:196° C.).

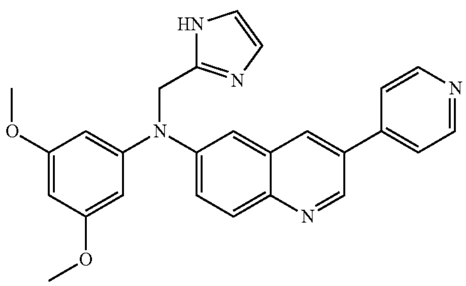
Analogous preparation of compound 55



1.86 HCl

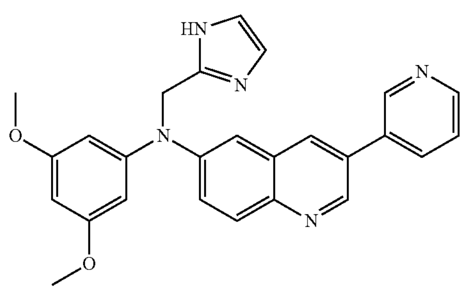
starting from compound 56

Analogous preparation of compound 57



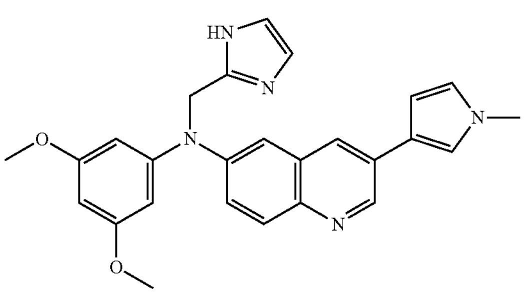
starting from compound 58

Analogous preparation of compound 59



starting from compound 60

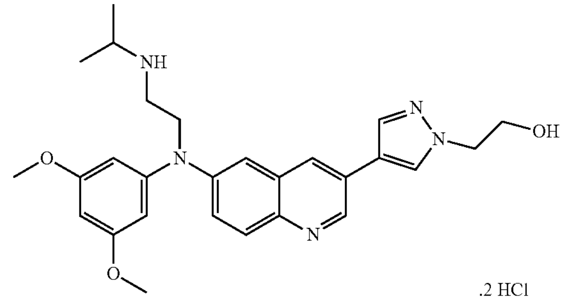
Analogous preparation of compound 62



starting from compound 63

Conversion C3

Preparation of Compound 13

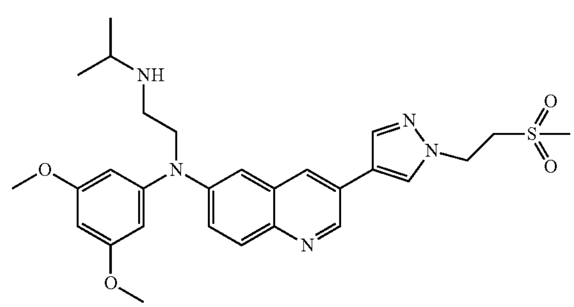


.2 HCl

A solution of compound 21 (0.46 g; 1.07 mmol) ethylene carbonate (104 mg; 0.18 mmol) and sodium hydroxide (4 mg; 0.107 mmol) in DMF (8.3 mL) was purged with argon and stirred at reflux for 2 hours. LC/MS showed a full conversion. The reaction mixture was cooled down to room temperature. A saturated solution of ammonium chloride was added and the mixture was stirred at room temperature for 20 min. The organic layer was decanted and successively washed with a saturated solution of sodium bicarbonate (20 mL), brine (50 mL), dried over $MgSO_4$, filtered and evaporated to afford a brown yellow solid. The residue was purified by chromatography over silica gel (mobile phase; phase gradient from 95% DCM, 5% MeOH to 90% DCM, 10% MeOH). The product fractions were collected and the solvent was evaporated to provide a yellow foam (370 mg, 73%). The product was triturated in acetonitrile and the suspension was filtered off to provide 62 mg (12%) of compound 13. The filtrate was concentrated under reduced pressure to afford 308 mg of a yellow foam. (0.308 g, 0.648 mmol) was dissolved in DCM (3 ml) and HCl (2.2 ml, 2M/Et_2O, 6.476 mmol) was added dropwise at room temperature. The orange suspension was stirred at room temperature for 1 hour. The reaction mixture was concentrated under reduced pressure. The resulting solid was triturated with Et_2O and filtered off on glass-frit, yielding 250 mg of compound 13 (75%) as a chlorohydrate (MP: 86-115° C.).

Conversion C4

Preparation of Compound 14

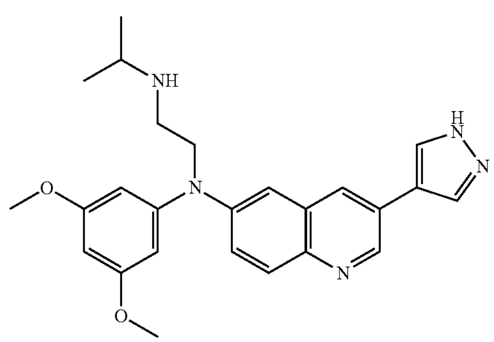


The reaction was performed in anhydrous conditions under argon.

To a solution of compound 21 (0.618 g, 1.4 mmol) and K_2CO_3 (0.396 g, 2.9 mmol) in DMF (6.4 ml) was added dropwise methylsulfonylethene (0.14 ml, 1.6 mmol) at room temperature. The yellow solution was stirred at 70° C. for 1 hour. A saturated solution of ammonium chloride (10 ml) was added and the aqueous layer was extracted with EtOAc (20 ml). The organic layer was washed with brine (50 ml), dried over Na_2SO_4, filtered and concentrated. The crude product was purified by chromatography over silica gel (mobile phase; phase gradient from 95% DCM, 5% MeOH to 90% DCM, 10% MeOH). The product fractions were collected and the solvents were evaporated. The residue was triturated with diethylether and the suspension was filtered off, yielding 616 mg of compound 14 (80%) (MP: 129° C. (DSC)).

Conversion C5

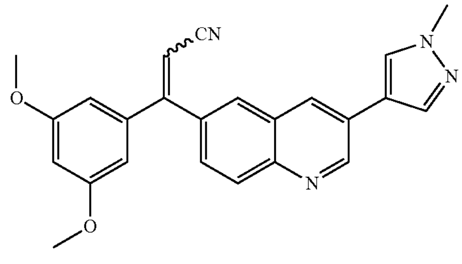
Preparation of Compound 21



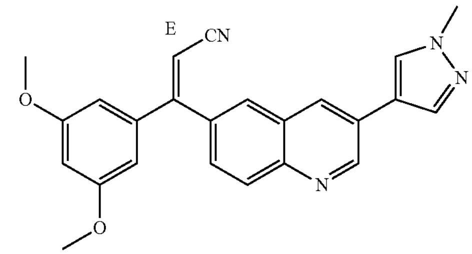
To a solution of compound 22 (1.56 g, 3.0 mmol) in MeOH (282 ml) was added dropwise HCl (37%; 9.3 ml) at room temperature. The orange solution was stirred at room temperature for 1 hour. The TLC showed a full conversion into the desired compound. The reaction mixture was cooled to 0° C. Then, a saturated solution of sodium carbonate was added until a pH=12 and the mixture was stirred at room temperature for 1 hour. The aqueous layer was extracted twice with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford a yellow gum (1.7 g). The crude product was purified by chromatography over silica gel (mobile phase, gradient from 95% DCM, 5% MeOH to 85% DCM, 15% MeOH). The product fractions were collected and the solvent was evaporated, yielding 1.068 g of compound 21 (82%).

Conversion C6

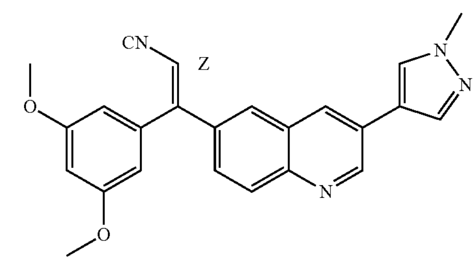
Preparation of Compound 28,



compound 29 and



compound 30



Diethyl cyanomethylphosphonate (0.249 mL; 1.53 mmol) was added in anhydrous conditions under Ar atmosphere to a suspension of sodium hydride (61.4 mg; 1.53 mmol; 60% in oil) in THF (1.5 mL) at 0° C. After 1 hour at room temperature, a solution of compound 31 (191 mg; 0.51 mmol) in THF (5.1 mL) was added drop wise and the reaction mixture was heated to reflux for 2 h 30. It was then diluted with water (10 mL) and extracted with DCM (3×10 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure.

The residue (368 mg; red oil) was purified by chromatography over silica gel (SiOH, 15-40 μm, eluent: EtOAc/MeOH:99/1). After evaporation of the solvent, 3 different fractions were obtained:

Fraction A: 187 mg of compound 28 (colorless oil; mixture of compound 29 and compound 30:6/4)

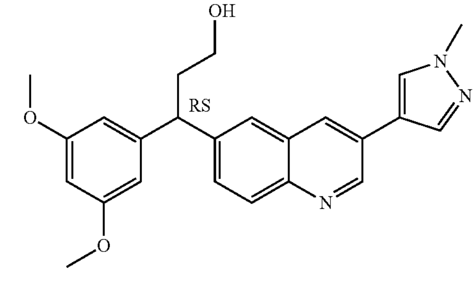
Fraction B: 9 mg of compound 29 (colorless oil)

Fraction C: 8 mg of compound 30 (colorless oil)

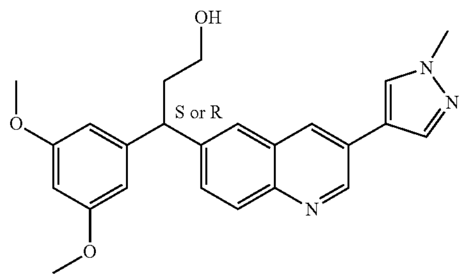
Fraction A was purified by achiral SFC (stationary phase: DIETHYLAMINOPROPYL 5 μm 150×21.2 mm; mobile phase: 90% CO_2, 10% MeOH). The product fractions were collected and evaporated to dryness yielding additional 53 mg of compound 29, M.P.: 86° C. (gum, Kofler), and additional 31 mg of compound 30. MP: 166° C. (Kofler). Based on fraction A, B and C, the overall yield is 73%

Conversion C7

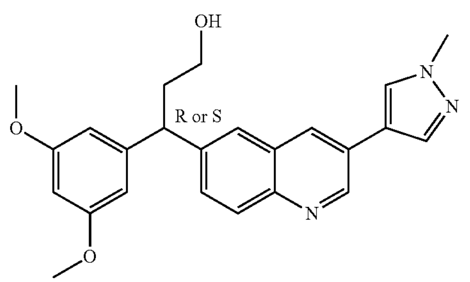
Preparation of compound 34,



compound 35 and



compound 36

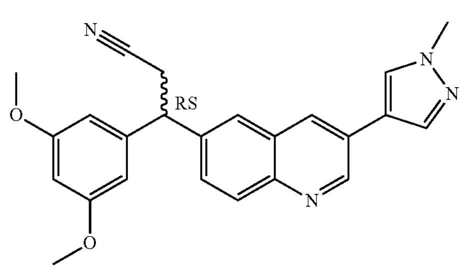


Lithium aluminium hydride (67.7 mg; 1.78 mmol) was added portion wise to a solution of mixture of compound 32 and compound 33 (385 mg; 0.892 mmol) in THF (10 mL) at 0° C. and the reaction mixture was stirred for 1 hour 20 minutes at this temperature. EtOAc (20 mL) was added slowly followed by water (30 mL) and the mixture was extracted by DCM (2×80 mL). The organic layers were combined, dried over Na_2SO_4, filtered and concentrated.

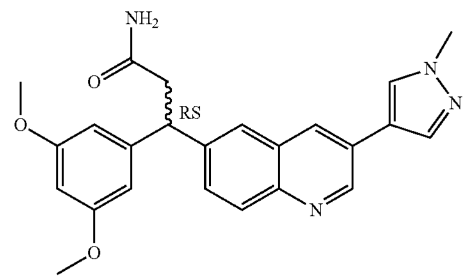
The residue (385 mg; pale yellow gum) was purified by chromatography over silica gel (15-40 μm, eluent: DCM/MeOH: 98/2). The product fractions were mixed and the solvent was evaporated to give 247 mg of a pale yellow gum which was sonicated in ACN (5 mL). The resulting solid was filtered off on a glass frit, rinsed with ACN (2×5 mL) and dried under vacuum (80° C., 16 h) to afford 117 mg (32%) of compound 34 as a white solid. MP=131° C. (DSC).

80 mg of this fraction were purified by chiral SFC (stationary phase: CHIRALCEL OJ-H 5 μm 250×20 mm; mobile phase: 65% CO_2, 35% iPrOH). The product fractions were collected and evaporated to dryness yielding 37 mg of compound 35, M.P.: gum 56° C. (Kofler) and 38 mg of compound 36. M.P.: gum at 56° C. (Kofler).

Conversion C8



Preparation of compound 39 and



compound 40

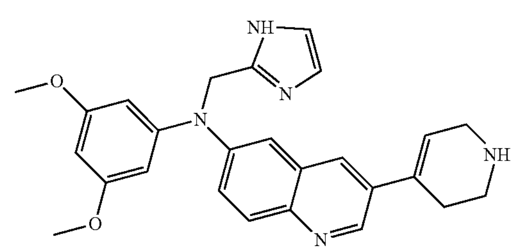
Sodium borohydride (0.064 g; 1.69 mmol) was added at room temperature under argon atmosphere to a solution of compound 28 (0.096 g; 0.242 mmol) in pyridine (1.5 mL) and MeOH (0.5 mL). The reaction mixture was refluxed for 18 hours and cooled to room temperature. Additionnal sodium borohydride (0.018 g; 0.484 mmol) was added and the reaction mixture was refluxed for 5 hours more, quenched with ice water (15 mL) and extracted with EtOAc (3×10 mL). The combined organic layers were dried over Na_2SO_4, filtered and evaporated to dryness. The residue (100 mg) was purified by chromatography over silica gel (irregular SiOH, 15-40 μm; mobile phase: gradient from 2% MeOH, 98% DCM to 10% MeOH, 90% DCM). The product fractions were collected and evaporated to dryness to give 2 fractions:

Fraction A: 0.045 g which were triturated in Et_2O to give 0.032 g (33%) of compound 39. M.P.: 172° C. (DSC)

Fraction B: 0.011 g (11%) of compound 40.

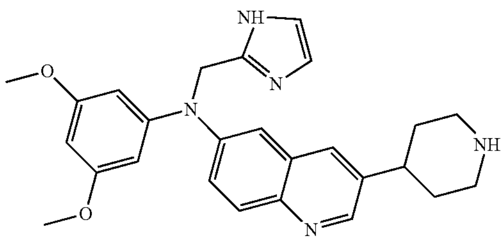
Conversion C9

Preparation of Compound 46



A mixture of compound 45 (0.25 g; 0.385 mmol) and 6N HCl (5.14 mL) in dioxane (5.14 mL) was heated at 100° C. overnight. The mixture was basified by solid K_2CO_3 and evaporated till dryness. The residue was taken up by DCM/MeOH/NH4OH (90/10/1) and filtered. The filtrate was evaporated. The residue was purified by chromatography over silica gel (irregular SiOH, 24 g; 15-40 μm, mobile phase (90% DCM, 10% MeOH, 1% NH_4OH). The pure fractions were mixed and the solvent was evaporated. The residue was taken up by Et_2O, filtered and dried to give 36 mg (21%) of compound 46. MP: gum at 110° C. (Kofler)

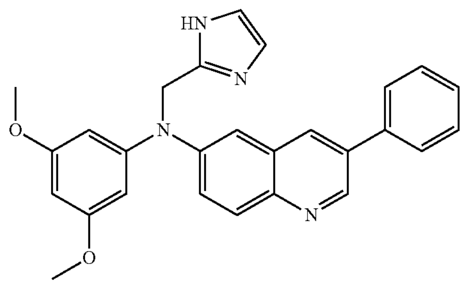
Analogous preparation of compound 48a



starting from compound 49

Conversion C9a

Preparation of Compound 52



To a solution of compound 53 (490 mg; 0.77 mmol) in ACN (29.5 mL) was added drop wise at 5° C., HCl 4M in dioxane (1.92 ml; 7.66 mmol). The reaction mixture was then heated at 50° C. for 18 h and then concentrated under reduced pressure. The reaction mixture was taken up with DCM and washed with 10% aqueous K_2CO_3 and brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue (360 mg) was purified by chromatography over silica gel (irregular SiOH, 15-40 μm 30 g, Mobile phase: 0.1% NH_4OH, 97% DCM, 3% MeOH, flow rate 20 ml/min). The pure fraction were mixed and concentrated under reduced pressure to afford 90 mg of an intermediate compound which was taken up in Et_2O. The precipitate was filtered to afford 59 mg of compound 52 (18%). MP: 133° C. (DSC)

The following compounds were prepared according to reaction protocols of one of the above Examples using alternative starting materials as appropriate.

In the table =CX (or =BX) indicates that the preparation of this compound is described in Conversion X (or Method BX).

In the table ~CX (or ~BX) indicates that this compound is prepared according to Conversion X (or Method BX).

As understood by a person skilled in the art, compounds synthesised using the protocols as indicated may exist as a solvate e.g. hydrate, and/or contain residual solvent or minor impurities. Compounds isolated as a salt form, may be integer stoichiometric i.e. mono- or di-salts, or of intermediate stoichiometry.

TABLE A1

physico-chemical data

If physio-chemical data were generated multiple times for a compound then all data is listed

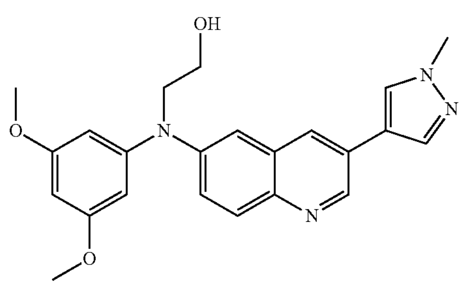
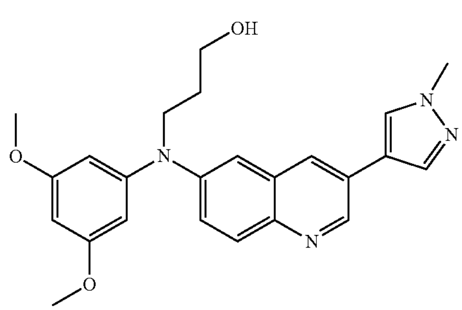
Co. No.	Compound structure	Method	Melting Point (° C.)	(Kofler (K) or DSC)	HPLC Rt (min)	MS M+ (H^+)	LC/GC/MS method
3		=B2	195	K	2.46	405	1
4		=B3	184 (gum)	K	2.52	419	1

TABLE A1-continued

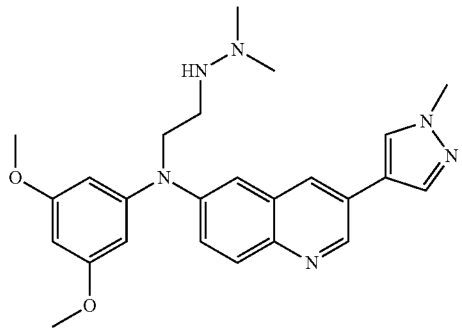
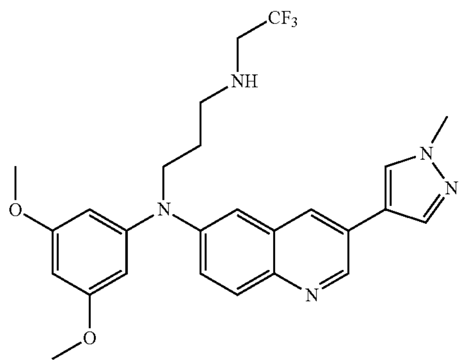
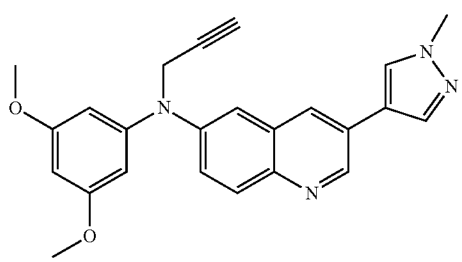
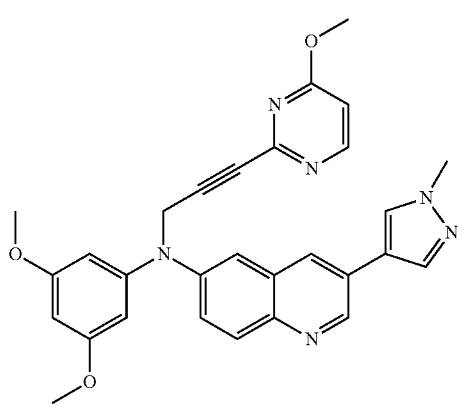
physico-chemical data If physio-chemical data were generated multiple times for a compound then all data is listed							
Co. No.	Compound structure	Method	Melting Point (° C.)	(Kofler (K) or DSC)	HPLC Rt (min)	MS M+ (H+)	LC/GC/ MS method
1	 as a HCl salt	=B1	227	K	2.31	446	1
5	 as a HCl salt	=B4	186 (gum)	K	3.05	500	1
6		=B5	142	K	2.86	399	1
16		=C1	203	DSC	2.9	507	1

TABLE A1-continued

physico-chemical data
If physio-chemical data were generated multiple times for a compound then all data is listed

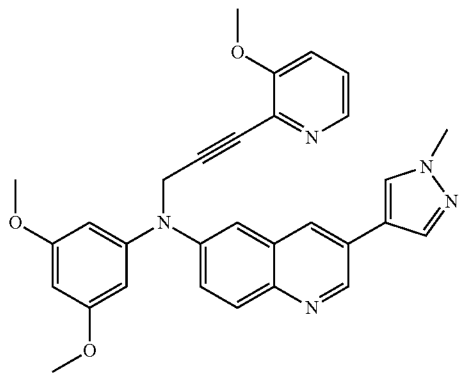
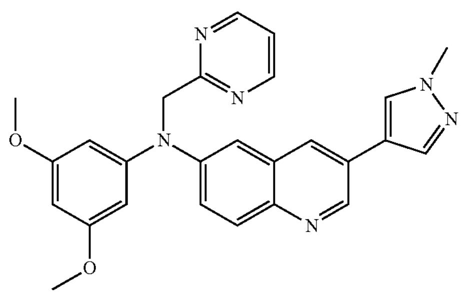
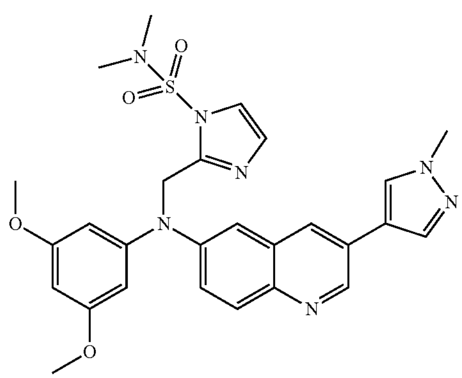
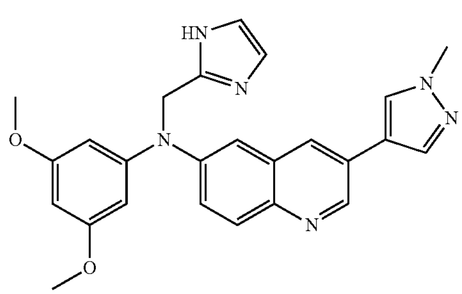
Co. No.	Compound structure	Method	Melting Point (° C.)	(Kofler (K) or DSC)	HPLC Rt (min)	MS M+ (H+)	LC/GC/MS method
17		~C1	155	DSC	2.81	506	1
8		=B7	151	DSC	2.63	453	1
9		~B7	110 (gum)		2.83	548	1
18		=C2	198	DSC	2.35	441	1

TABLE A1-continued

physico-chemical data
If physio-chemical data were generated multiple times for a compound then all data is listed

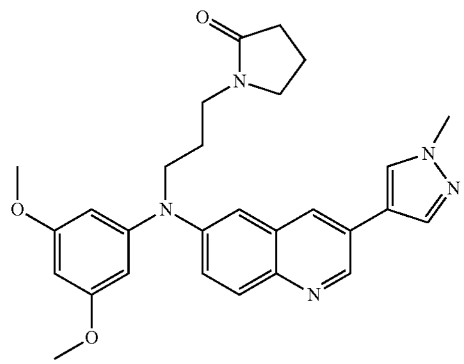
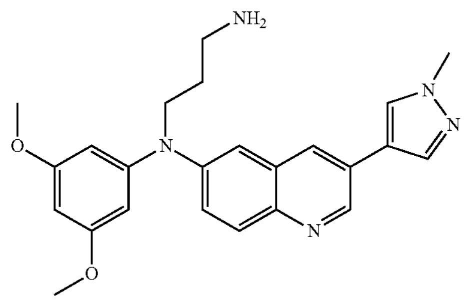
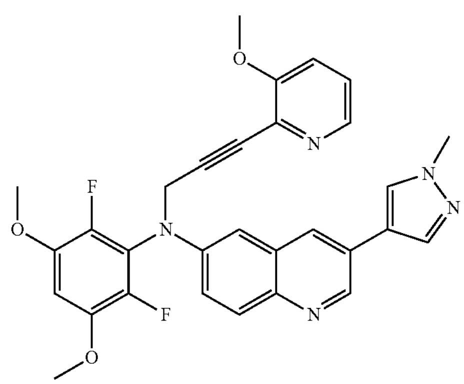
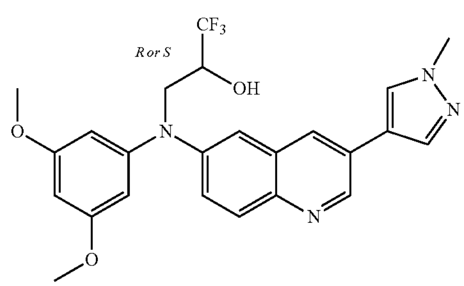
Co. No.	Compound structure	Method	Melting Point (° C.)	(Kofler (K) or DSC)	HPLC Rt (min)	MS M+ (H⁺)	LC/GC/MS method
10	 as a HCl salt	=B8	142	K	2.59	486	1
11		=B9			2.13	4.18	1
27		~C1	184	DSC	2.72	548	1
24		=B13 R or S	116	K	2.88	473	1

TABLE A1-continued

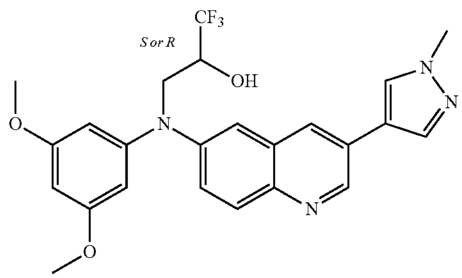
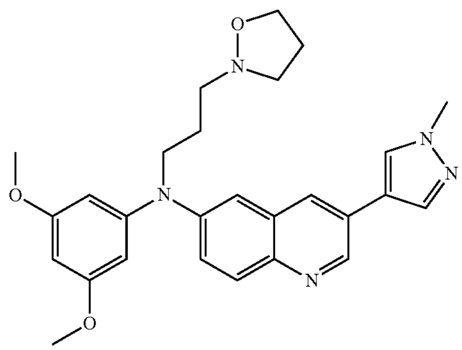
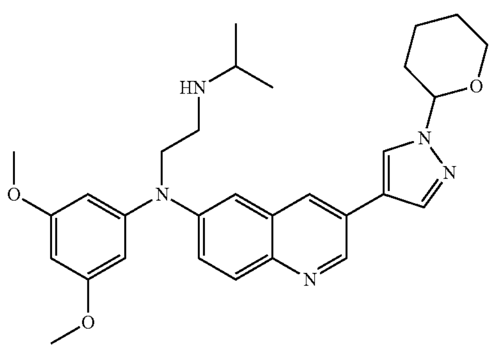
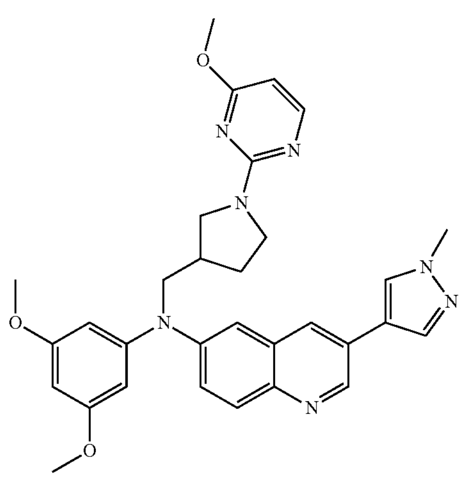
Co. No.	Compound structure	Method	Melting Point (° C.)	(Kofler (K) or DSC)	HPLC Rt (min)	MS M+ (H+)	LC/GC/MS method
	physico-chemical data If physio-chemical data were generated multiple times for a compound then all data is listed						
25		=B13 S or R	119	K	2.88	473	1
19		~B4	103	DSC	2.82	474	1
22		=B12			10.11	516	3
7		=B6	132	DSC	3.19	552	1

TABLE A1-continued

physico-chemical data
If physio-chemical data were generated multiple times for a compound then all data is listed

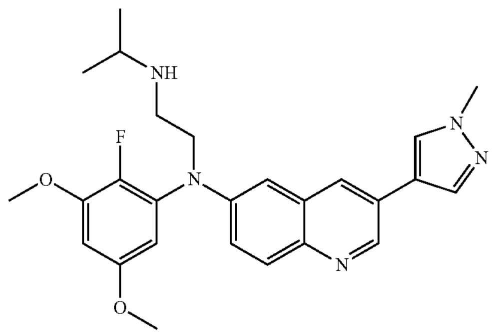
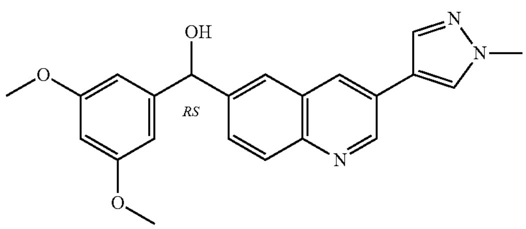
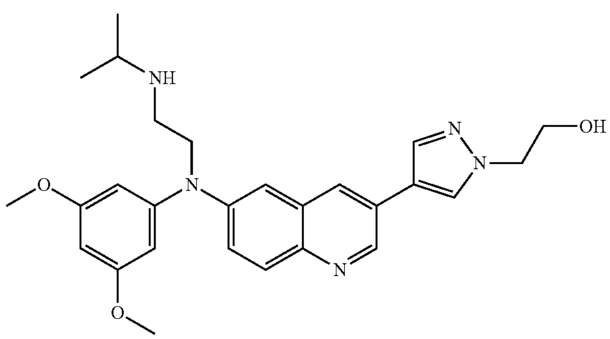
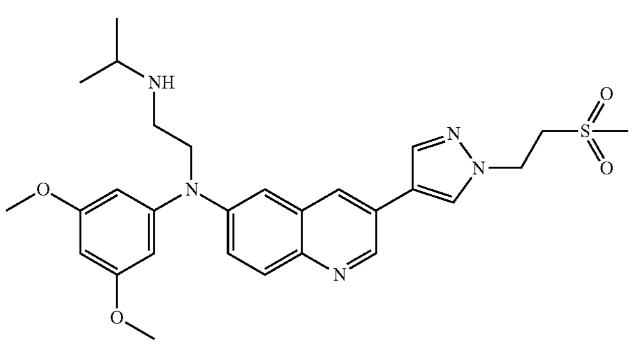
Co. No.	Compound structure	Method	Melting Point (° C.)	(Kofler (K) or DSC)	HPLC Rt (min)	MS M+ (H+)	LC/GC/MS method
2		~B1	70 (gum)		2.28	464	1
12		=B10	183-192		12.31	336	2
13	 as a HCl salt	=C3	86-115° C.	Buchi M-560	9.16	476	3
14		=C4	129	DSC	11.58	538	2

TABLE A1-continued

physico-chemical data
If physio-chemical data were generated multiple times for a compound then all data is listed

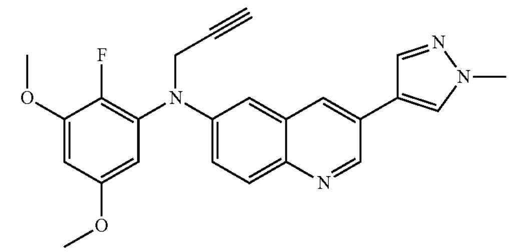
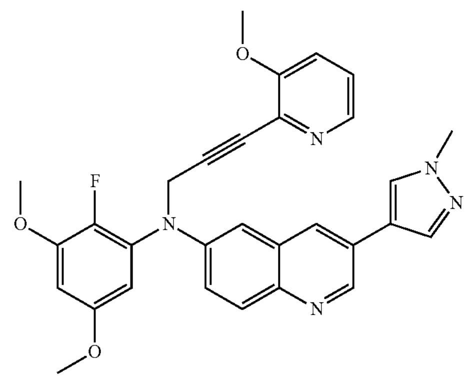
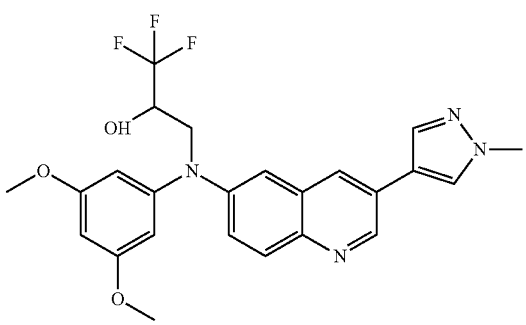
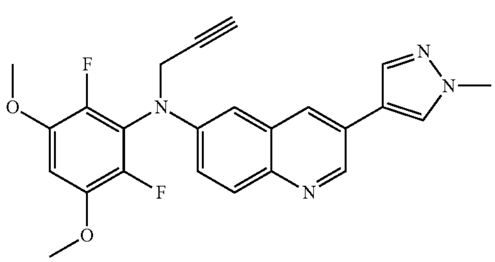
Co. No.	Compound structure	Method	Melting Point (° C.)	(Kofler (K) or DSC)	HPLC Rt (min)	MS M+ (H+)	LC/GC/MS method
15		=B11	120	K			
26		~C1	142	K	2.74	524	1
23		=B13					
20		~B11					

TABLE A1-continued

physico-chemical data
If physio-chemical data were generated multiple times for a compound then all data is listed

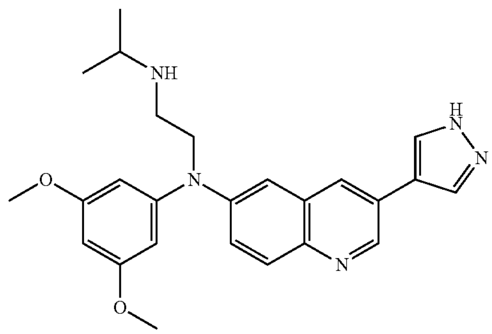
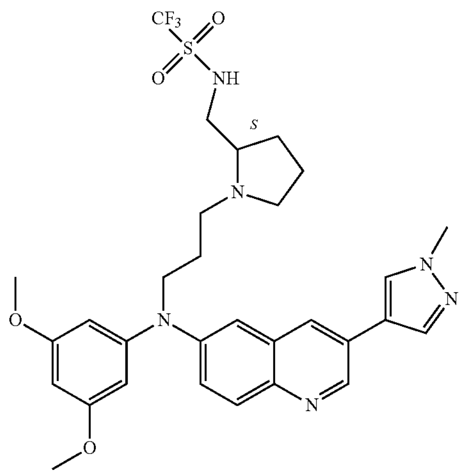
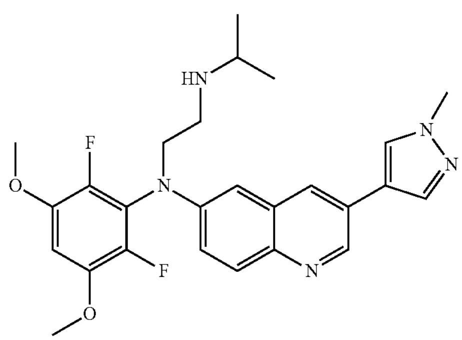
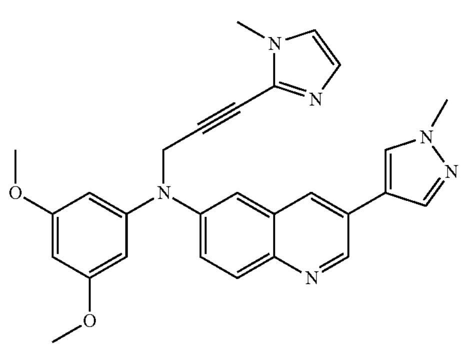
Co. No.	Compound structure	Method	Melting Point (° C.)	(Kofler (K) or DSC)	HPLC Rt (min)	MS M+ (H+)	LC/GC/MS method
21		=C5			11.49	432	1
47		~B8	115	DSC	2.66	633	1
42		=B1a	75	K	2.29	482	1
48		~C1	160	K	2.63	479	1

TABLE A1-continued

physico-chemical data
If physio-chemical data were generated multiple times for a compound then all data is listed

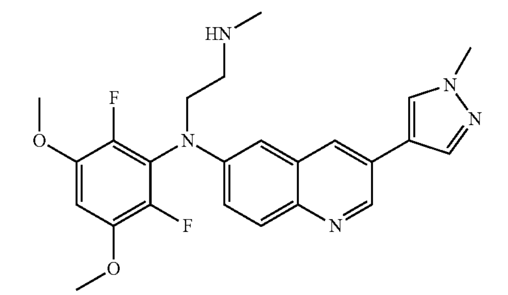
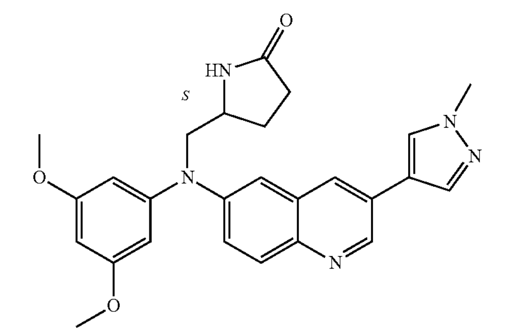
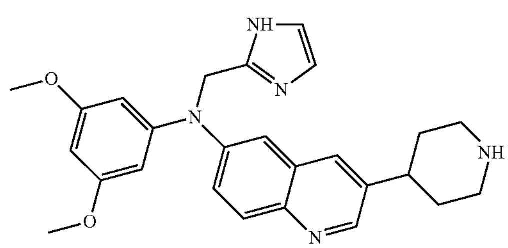
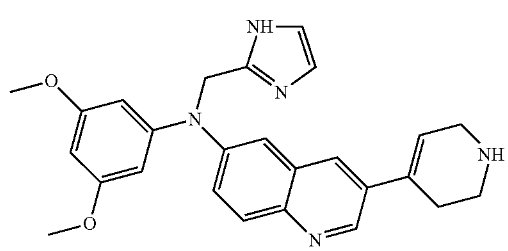
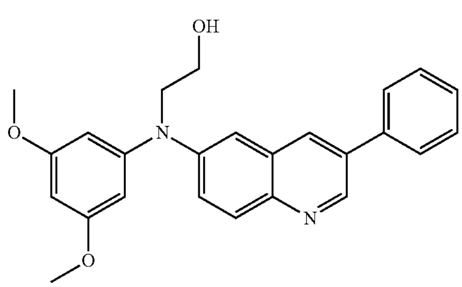
Co. No.	Compound structure	Method	Melting Point (° C.)	(Kofler (K) or DSC)	HPLC Rt (min)	MS M+ (H+)	LC/GC/MS method
43	 as a HCl salt	=B1b	180 (gum)	K	2.11	454	1
44		B17	108 (gum)	K	2.39	458	1
48a		~C9	Gum at 84	K	1.97	444	1
46		=C9	Gum at 110	K	1.98	442	1
50		=B3a	111	DSC	3.03	401	1

TABLE A1-continued

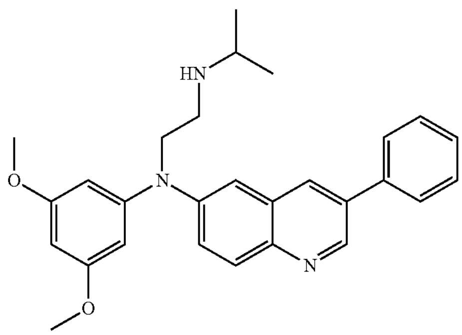
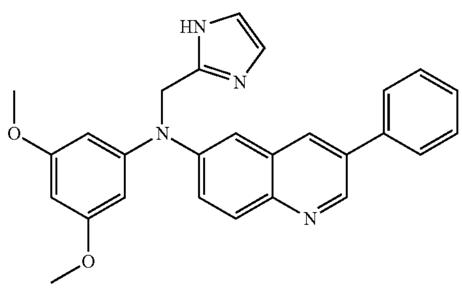
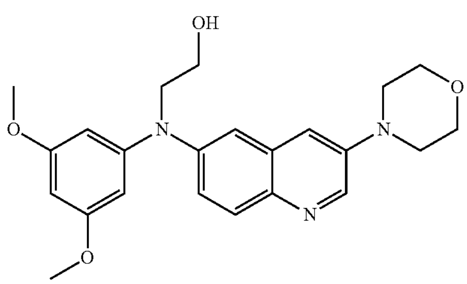
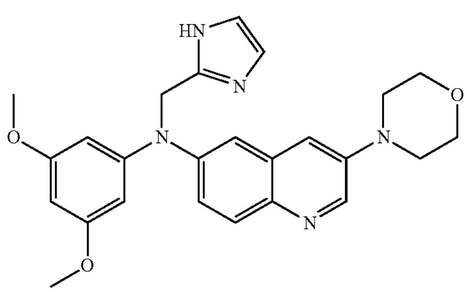
physico-chemical data If physio-chemical data were generated multiple times for a compound then all data is listed							
Co. No.	Compound structure	Method	Melting Point (° C.)	(Kofler (K) or DSC)	HPLC Rt (min)	MS M+ (H^+)	LC/GC/MS method
51	 as a HCl salt	B1	180° C. (gum)	K	2.87	442	1
52		B9a	133	DSC	2.82	437	1
54		~B3a	118	DSC	2.48	410	1
55	 as a HCl salt		220	K	2.35	446	1

TABLE A1-continued

physico-chemical data
If physio-chemical data were generated multiple times for a compound then all data is listed

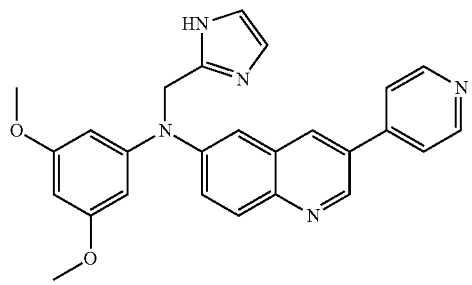
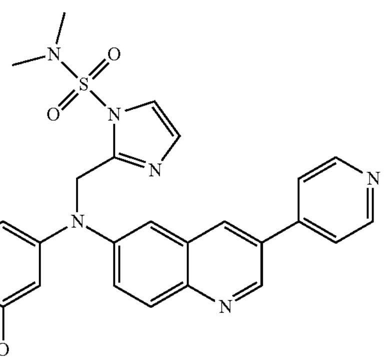
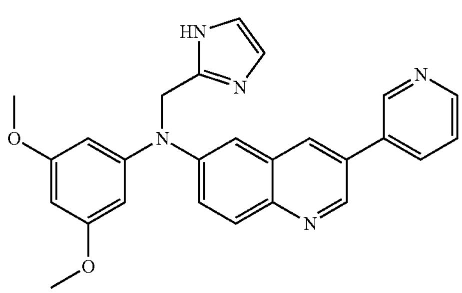
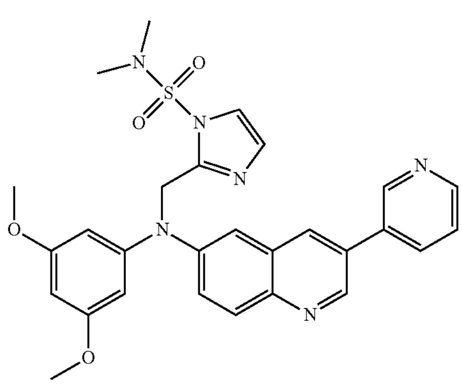
Co. No.	Compound structure	Method	Melting Point (° C.)	(Kofler (K) or DSC)	HPLC Rt (min)	MS M+ (H+)	LC/GC/MS method
57			113-126	Buchi M-560	8.79	438	3
58			161	DSC	10.51	545	3
59			110-123	Buchi M-560	8.7	438	3
60			82-86	Buchi M-560	10.64	545	3

TABLE A1-continued

physico-chemical data
If physio-chemical data were generated multiple times for a compound then all data is listed

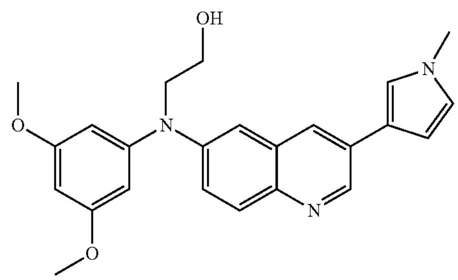
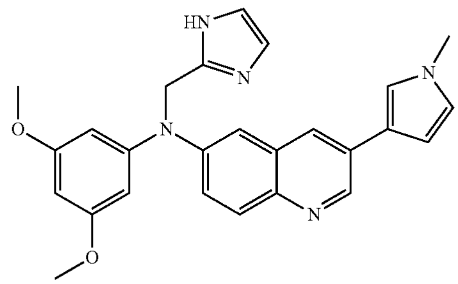
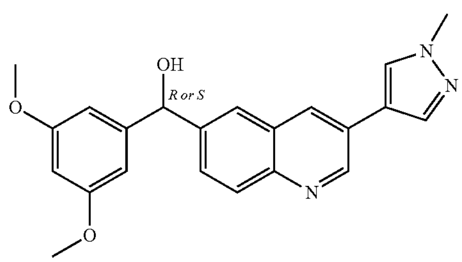
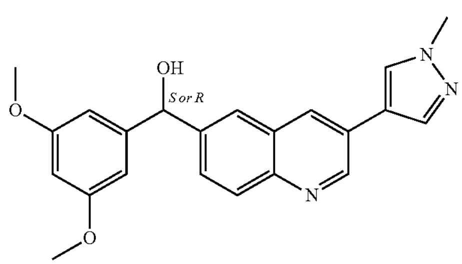
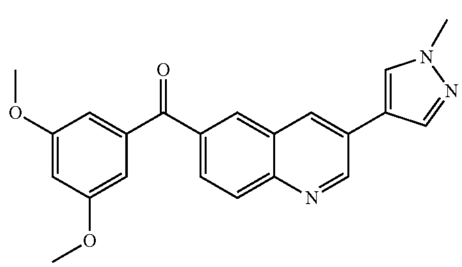
Co. No.	Compound structure	Method	Melting Point (° C.)	(Kofler (K) or DSC)	HPLC Rt (min)	MS M+ (H+)	LC/GC/MS method
61			158	DSC	2.75	404	1
62			197	DSC	2.60	440	1
38			174	K	2.32	376	1
37			174	K	2.32	376	1
31			190	K	2.76	374	1

TABLE A1-continued

physico-chemical data
If physio-chemical data were generated multiple times for a compound then all data is listed

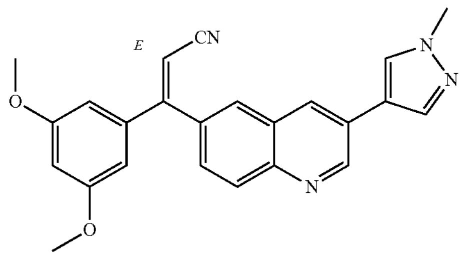
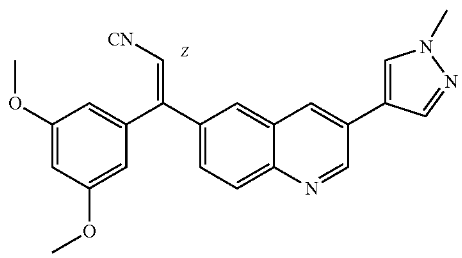
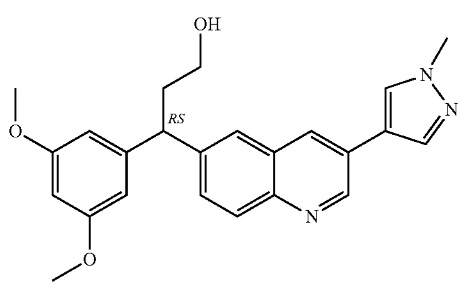
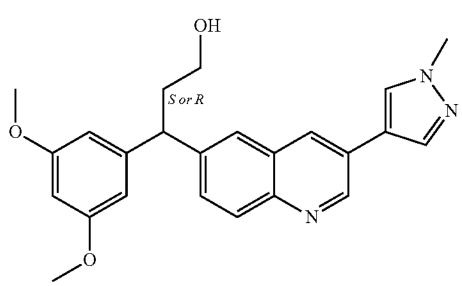
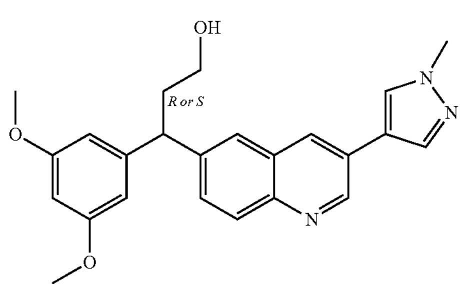
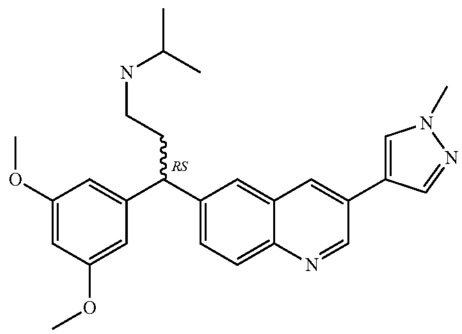
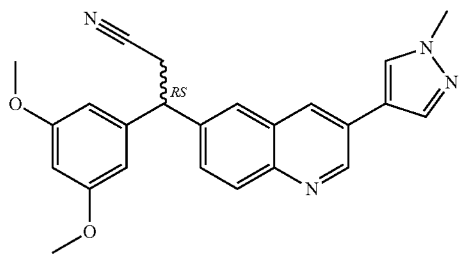
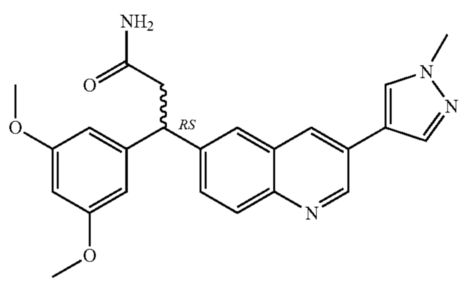
Co. No.	Compound structure	Method	Melting Point (° C.)	(Kofler (K) or DSC)	HPLC Rt (min)	MS M+ (H$^+$)	LC/GC/ MS method
29			Gum at 86	K	2.78	397	1
30			166	K	2.73	397	1
34			131	DSC	9.81	404	3
35			Gum at 56	K	2.34	404	1
36			Gum at 56	K	2.34	404	1

TABLE A1-continued

physico-chemical data
If physio-chemical data were generated multiple times for a compound then all data is listed

Co. No.	Compound structure	Method	Melting Point (° C.)	(Kofler (K) or DSC)	HPLC Rt (min)	MS M+ (H+)	LC/GC/MS method
41	 as a HCl salt		>300	DSC	9.26	445	3
39			172	DSC	10.53	399	3
40			—	—	9.35	417	3

Analytical Part

LC/GC/NMR

The LC/GC data reported in Table A1 were determined as follows.

General Procedure A

The LC measurement was performed using a UPLC (Ultra Performance Liquid Chromatography) Acquity (Waters) system comprising a binary pump with degasser, an autosampler, a diode-array detector (DAD) and a column as specified in the respective methods below, the column is hold at a temperature of 40° C. Flow from the column was brought to a MS detector. The MS detector was configured with an electrospray ionization source. The capillary needle voltage was 3 kV and the source temperature was maintained at 130° C. on the Quattro (triple quadrupole mass spectrometer from Waters). Nitrogen was used as the nebulizer gas. Data acquisition was performed with a Waters-Micromass MassLynx-Openlynx data system.

Method 1

In addition to the general procedure A: Reversed phase UPLC was carried out on a Waters Acquity BEH (bridged ethylsiloxane/silica hybrid) C18 column (1.7 μm, 2.1×100 mm) with a flow rate of 0.343 ml/min. Two mobile phases (mobile phase A: 95% 7 mM ammonium acetate/5% acetonitrile; mobile phase B: 100% acetonitrile) were employed to run a gradient condition from 84.2% A and 15.8% B (hold for 0.49 minutes) to 10.5% A and 89.5% B in 2.18 minutes, hold for 1.94 min and back to the initial conditions in 0.73 min, hold for 0.73 minutes. An injection volume of 2 μl was used. Cone voltage was 20V for positive and negative ionization mode. Mass spectra were acquired by scanning from 100 to 1000 in 0.2 seconds using an interscan delay of 0.1 seconds.

General Procedure B

The HPLC measurement was performed using an HPLC 1100/1200 (Agilent) system comprising a quaternary pump with degasser, an autosampler, a diode-array detector (DAD) and a column as specified in the respective methods below, the column is held at a room temperature. The MS detector (MS-Agilent simple quadripole) was configured with an electrospray-APCI ionization source. Nitrogen was used as the nebulizer gas. Data acquisition was performed with a Chemstation data system.

Method 2

In addition to the general procedure B: Reversed phase HPLC was carried out on a Nucleosil C18 column (3 μm, 3×150 mm) with a flow rate of 0.42 ml/min. Two mobile phases (mobile phase A: Water TFA 0.1%; mobile phase B: 100% acetonitrile) were employed to run a gradient condition from 98% A for 3 minutes, to 100% B in 12 minutes, 100% B for 5 minutes, then back to 98% A in 2 minutes, and reequilibrated with 98% A for 6 minutes. An injection volume of 2 μl was used. The capillary voltage was 2 kV, the corona discharge was held at 1 μA and the source temperature was maintained at 250° C. A variable voltage was used for the fragmentor. Mass spectra were acquired in electrospray ionization and APCI in positive mode, by scanning from 100 to 1100 amu.

Method 3

In addition to the general procedure B: Reversed phase HPLC was carried out on a Agilent Eclipse C18 column (5 μm, 4.6×150 mm) with a flow rate of 1 ml/min. Two mobile phases (mobile phase A: Water TFA 0.1%; mobile phase B: 100% acetonitrile) were employed to run a gradient condition from 98% A for 3 minutes, to 100% B in 12 minutes, 100% B for 5 minutes, then back to 98% A in 2 minutes, and reequilibrated with 98% A for 6 minutes. An injection volume of 2 μl was used. The capillary voltage was 2 kV, the corona discharge was held at 1 μA and the source temperature was maintained at 250° C. A variable voltage was used for the fragmentor. Mass spectra were acquired in electrospray ionization and APCI in positive mode, by scanning from 80 to 1000 amu.

DSC:

Melting point (M.P.) were taken with a Kofler hot bar or a Büchi Melting Point M-560 but also for a number of compounds, melting points (m.p.) were determined with a DSC1 Star^e System (Mettler-Toledo). Melting points were measured with a temperature gradient of 10° C./minute. Maximum temperature was 350° C. Values are peak values."

OR:

Optical Rotation is measured with a polarimeter 341 Perkin Elmer.

The polarized light is passed through a sample with a path length of 1 decimeter and a sample concentration of 0.250 to 0.500 gram per 100 milliliters.

$$[\alpha]_d^T\text{:(red rotation}\times 100)/(1.000\ \text{dm}\times\text{concentration}).$$

^{d} is sodium D line (589 nanometer).

T is the temperature (° C.).

OR:

Compound 47: $[\alpha]_d$: −28.16° (589 nm, c 0.245 w/v %, DMF, 20° C.)

The below NMR experiments were carried out using a Bruker Avance 500 and a Bruker Avance DRX 400 spectrometers at ambient temperature, using internal deuterium lock and equipped with reverse triple-resonance (^{1}H, ^{13}C, ^{15}N TXI) probe head for the 500 MHz and with reverse double-resonance (^{1}H, ^{13}C, SEI) probe head for the 400 MHz. Chemical shifts (δ) are reported in parts per million (ppm).

Compound 1:

^{1}H NMR (500 MHz, DMSO-d6) δ 9.16 (s, 1H), 9.05 (s, 2H), 8.71 (br.s, 1H), 8.42 (s, 1H), 8.11 (s, 1H), 8.02 (d, J=9.3 Hz, 1H), 7.60 (d, J=9.3 Hz, 1H), 7.50 (d, J=2.7 Hz, 1H), 6.42-6.58 (m, 3H), 4.17 (t, J=7.6 Hz, 2H), 3.92 (s, 3H), 3.75 (s, 6H), 3.34 (spt, J=6.4 Hz, 1H), 3.15 (m, 2H), 1.25 (d, J=6.4 Hz, 6H).

Compound 16:

^{1}H NMR (500 MHz, DMSO-d6) δ 9.00 (d, J=2.1 Hz, 1H), 8.43 (d, J=5.9 Hz, 1H), 8.38 (s, 1H), 8.35 (d, J=2.1 Hz, 1H), 8.08 (s, 1H), 7.87 (d, J=9.1 Hz, 1H), 7.46 (d, J=2.6 Hz, 1H), 7.40 (dd, J=9.1, 2.6 Hz, 1H), 6.91 (d, J=5.9 Hz, 1H), 6.40 (d, J=2.1 Hz, 2H), 6.33 (t, J=2.1 Hz, 1H), 4.93 (s, 2H), 3.90 (s, 3H), 3.86 (s, 3H), 3.72 (s, 6H).

Compound 17:

^{1}H NMR (500 MHz, DMSO-d6) δ 9.00 (d, J=2.2 Hz, 1H), 8.37 (s, 1H), 8.33 (d, J=2.2 Hz, 1H), 8.08 (s, 1H), 8.06 (d, J=4.4 Hz, 1H), 7.86 (d, J=9.1 Hz, 1H), 7.48-7.43 (m, 2H), 7.41 (dd, J=9.1, 2.6 Hz, 1H), 7.33 (dd, J=8.5, 4.4 Hz, 1H), 6.42 (d, J=2.2 Hz, 2H), 6.32 (t, J=2.2 Hz, 1H), 4.89 (s, 2H), 3.90 (s, 3H), 3.76 (s, 3H), 3.72 (s, 6H).

Compound 42:

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.88 (d, J=2.02 Hz, 1H), 8.32 (s, 1H), 8.22 (d, J=2.02 Hz, 1H), 8.03 (s, 1H), 7.78 (d, J=9.09 Hz, 1H), 7.07 (dt, J=2.78, 9.09 Hz, 2H), 6.96 (d, J=2.78 Hz, 1H), 3.92 (s, 6H), 3.90 (s, 3H), 3.76 (t, J=7.07 Hz, 2H), 2.78 (t, J=7.07 Hz, 2H), 2.63-2.72 (m, 1H), 1.57 (br. s., 1H), 0.94 (d, J=6.06 Hz, 6H)

Compound 43:

^{1}H NMR (500 MHz, DMSO-d_6) δ 9.23 (s, 1H), 9.19 (br. s., 2H), 8.83 (br. s., 1H), 8.44 (s, 1H), 8.07-8.15 (m, 2H), 7.54 (d, J=8.20 Hz, 1H), 7.42 (br. s., 1H), 7.17 (t, J=8.20 Hz, 1H), 4.07-4.14 (m, 2H), 3.89-3.98 (m, 9H), 3.17 (br. s., 2H), 2.62 (t, J=5.20 Hz, 3H)

Compound 44:

^{1}H NMR (500 MHz, DMSO-d_6) δ 8.94 (d, J=2.21 Hz, 1H), 8.35 (s, 1H), 8.24 (d, J=2.21 Hz, 1H), 8.05 (s, 1H), 7.85 (s, 1H), 7.80 (d, J=8.83 Hz, 1H), 7.33 (dd, J=2.52, 8.83 Hz, 1H), 7.29 (d, J=2.52 Hz, 1H), 6.35 (d, J=2.21 Hz, 2H), 6.28 (t, J=2.21 Hz, 1H), 3.90 (s, 3H), 3.79-3.86 (m, 3H), 3.70 (s, 6H), 2.20-2.31 (m, 1H), 2.03-2.15 (m, 2H), 1.63-1.73 (m, 1H)

Compound 2:

^{1}H NMR (DMSO-d_6, 500 MHz): δ (ppm) 8.86 (d, J=2.2 Hz, 1H), 8.33 (s, 1H), 8.21 (d, J=2.2 Hz, 1H), 8.04 (s, 1H), 7.75 (d, J=9.1 Hz, 1H), 7.11 (dd, J=9.1, 2.7 Hz, 1H), 6.96 (d, J=2.7 Hz, 1H), 6.70 (dd, J=6.5, 3.0 Hz, 1H), 6.61 (dd, J=5.5, 3.0 Hz, 1H), 3.89 (s, 3H), 3.86 (s, 3H), 3.81 (t, J=6.9 Hz, 2H), 3.76 (s, 3H), 2.78 (t, J=6.9 Hz, 2H), 2.69 (spt, J=6.1 Hz, 1H), 1.74 (br. s., 1H), 0.94 (d, J=6.1 Hz, 6H)

Compound 46:

^{1}H NMR (DMSO-d_6, 500 MHz): δ (ppm) 11.91 (br. s., 1H), 8.87 (d, J=2.2 Hz, 1H), 8.01 (d, J=2.2 Hz, 1H), 7.80 (d, J=9.1 Hz, 1H), 7.54 (d, J=2.5 Hz, 1H), 7.45 (dd, J=9.1, 2.5 Hz, 1H), 7.00 (s, 1H), 6.83 (s, 1H), 6.50 (br. s., 1H), 6.39 (d, J=2.2 Hz, 2H), 6.21 (t, J=2.2 Hz, 1H), 4.99 (s, 2H), 3.68 (s, 6H), 3.40-3.47 (m, 2H), 2.96 (t, J=5.7 Hz, 2H), 2.72 (br. s., 1H), 2.44 (s, 2H)

Compound 29:

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.14 (1H, d, J=2.4 Hz), 8.24 (1H, d, J=2.4 Hz), 8.14 (1H, d, J=8.4 Hz), 8.04 (1H, d, J=2.0 Hz), 7.94 (1H, s), 7.83 (1H, s), 7.59 (1H, dd, J=8.4 Hz, J=2.0 Hz), 6.56 (1H, t, J=2.4 Hz), 6.44 (2H, d, J=2.4 Hz), 5.86 (1H, s), 4.02 (3H, s), 3.76 (6H, s).

Compound 30:

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.10 (1H, d, J=2.0 Hz), 8.14 (1H, d, J=2.0 Hz), 8.08 (1H, d, J=8.8 Hz), 7.91 (1H, s), 7.80 (1H, s), 7.73 (1H, d, J=2.0 Hz), 7.64 (1H, dd, J=8.8 Hz, J=2.0 Hz), 6.60 (3H, s), 5.89 (1H, s), 4.01 (3H, s), 3.81 (6H, s).

Pharmacological Part

Biological Assays A

FGFR1 (Enzymatic Assay)

In a final reaction volume of 30 μL, FGFR1 (h) (25 ng/ml) was incubated with 50 mM HEPES pH 7.5, 6 mM $MnCl_2$, 1 mM DTT, 0.1 mM Na_3VO_4, 0.01% Triton-X-100, 500 nM Btn-Flt3 and 5 μM ATP in the presence of compound (1% DMSO final). After incubation for 60 minutes at room temperature the reaction was stopped with 2.27 nM EU-anti P-Tyr, 7 mM EDTA, 31.25 nM SA-XL-665 and 0.02% BSA which was present for 60 minutes at room temperature. Time-Resolved Fluorescence Resonance Energy Transfer (TR-FRET) signal (ex340 nm. Em 620 nm, em 655 nm) was measured afterwards and results are expressed in RFU (Relative Fluorescence Units). In this assay, the inhibitory effect of different compound concentrations (range 10 μM to 0.1 nM) was determined and used to calculate an IC_{50} (M) and pIC_{50} (−log IC_{50}) value.

FGFR2 (Enzymatic Assay)

In a final reaction volume of 30 μL, FGFR2 (h) (150 ng/ml) was incubated with 50 mM HEPES pH 7.5, 6 mM $MnCl_2$, 1 mM DTT, 0.1 mM Na_3VO_4, 0.01% Triton-X-100, 500 nM Btn-Flt3 and 0.4 μM ATP in the presence of compound (1% DMSO final). After incubation for 60 minutes at room temperature the reaction was stopped with 2.27 nM EU-anti P-Tyr, 7 mM EDTA, 31.25 nM SA-XL-665 and 0.02% BSA which was present for 60 minutes at room temperature. Time-Resolved Fluorescence Resonance Energy Transfer (TR-FRET) signal (ex340 nm. Em 620 nm, em 655 nm) was measured afterwards and results are expressed in (Relative Fluorescence Units). In this assay, the inhibitory effect of different compound concentrations (range 10 μM to 0.1 nM) was determined and used to calculate an IC_{50} (M) and pIC_{50} (−log IC_{50}) value.

FGFR3 (Enzymatic Assay)

In a final reaction volume of 30 μL, FGFR3 (h) (40 ng/ml) was incubated with 50 mM HEPES pH 7.5, 6 mM $MnCl_2$, 1 mM DTT, 0.1 mM Na_3VO_4, 0.01% Triton-X-100, 500 nM Btn-Flt3 and 25 μM ATP in the presence of compound (1% DMSO final). After incubation for 60 minutes at room temperature the reaction was stopped with 2.27 nM EU-anti P-Tyr, 7 mM EDTA, 31.25 nM SA-XL-665 and 0.02% BSA which was present for 60 minutes at room temperature. Time-Resolved Fluorescence Resonance Energy Transfer (TR-FRET) signal (ex340 nm. Em 620 nm, em 655 nm) was measured afterwards and results are expressed in RFU (Relative Fluorescence Units). In this assay, the inhibitory effect of different compound concentrations (range 10 μM to 0.1 nM) was determined and used to calculate an IC_{50} (M) and pIC_{50} (−log IC_{50}) value.

FGFR4 (Enzymatic Assay)

In a final reaction volume of 30 μL, FGFR4 (h) (60 ng/ml) was incubated with 50 mM HEPES pH 7.5, 6 mM $MnCl_2$, 1 mM DTT, 0.1 mM Na_3VO_4, 0.01% Triton-X-100, 500 nM Btn-Flt3 and 5 μM ATP in the presence of compound (1% DMSO final). After incubation for 60 minutes at room temperature the reaction was stopped with 2.27 nM EU-anti P-Tyr, 7 mM EDTA, 31.25 nM SA-XL-665 and 0.02% BSA which was present for 60 minutes at room temperature. Time-Resolved Fluorescence Resonance Energy Transfer (TR-FRET) signal (ex340 nm. Em 620 nm, em 655 nm) was measured afterwards and results are expressed in RFU (Relative Fluorescence Units). In this assay, the inhibitory effect of different compound concentrations (range 10 μM to 0.1 nM) was determined and used to calculate an IC_{50} (M) and pIC_{50} (−log IC_{50}) value.

KDR (VEGFR2) (Enzymatic Assay)

In a final reaction volume of 30 μL, KDR (h) (150 ng/ml) was incubated with 50 mM HEPES pH 7.5, 6 mM $MnCl_2$, 1 mM DTT, 0.1 mM Na_3VO_4, 0.01% Triton-X-100, 500 nM Btn-Flt3 and 3 μM ATP in the presence of compound (1% DMSO final). After incubation for 120 minutes at room temperature the reaction was stopped with 2.27 nM EU-anti P-Tyr, 7 mM EDTA, 31.25 nM SA-XL-665 and 0.02% BSA which was present for 60 minutes at room temperature. Time-Resolved Fluorescence Resonance Energy Transfer (TR-FRET) signal (ex340 nm. Em 620 nm, em 655 nm) was measured afterwards and results are expressed in RFU (Relative Fluorescence Units). In this assay, the inhibitory effect of different compound concentrations (range 10 μM to 0.1 nM) was determined and used to calculate an IC_{50} (M) and pIC_{50} (−log IC_{50}) value.

Ba/F3-FGFR1 (Minus IL3 or Plus IL3) (Cellular Proliferation Assay)

In a 384 well plate, 100 n1 of compound dilution in DMSO was sprayed before adding 50 μl cell culture medium (phenol red free RPMI-1640, 10% FBS, 2 mM L-Glutamine and 50 μg/ml Gentamycin) containing 20000 cells per well of Ba/F3-FGFR1-transfected cells. Cells were put in an incubator at 37° C. and 5% CO_2. After 24 hours, 10 μl of Alamar Blue solution (0.5 mM $K_3Fe(CN)_6$, 0.5 mM $K_4Fe(CN)_6$, 0.15 mM Resazurin and 100 mM Phosphate Buffer) was added to the wells, incubated for 4 hours at 37° C. and 5% CO_2 before RFU's (Relative Fluorescence Units) (ex. 540 nm., em. 590 nm.) were measured in a fluororescence plate reader.

In this assay, the inhibitory effect of different compound concentrations (range 10 μM to 0.1 nM) was determined and used to calculate an IC_{50} (M) and pIC_{50} (−log IC_{50}) value. As a counterscreen the same experiment was performed in the presence of 10 ng/ml murine IL3.

Ba/F3-FGFR3 (Minus IL3 or Plus IL3) (Cellular Proliferation Assay)

In a 384 well plate, 100 nl of compound dilution in DMSO was sprayed before adding 50 μl cell culture medium (phenol red free RPMI-1640, 10% FBS, 2 mM L-Glutamine and 50 μg/ml Gentamycin) containing 20000 cells per well of Ba/F3-FGFR3-transfected cells. Cells were put in an incubator at 37° C. and 5% CO_2. After 24 hours, 10 μl of Alamar Blue solution (0.5 mM $K_3Fe(CN)_6$, 0.5 mM $K_4Fe(CN)_6$, 0.15 mM Resazurin and 100 mM Phosphate Buffer) was added to the wells, incubated for 4 hours at 37° C. and 5% CO_2 before RFU's (Relative Fluorescence Units) (ex. 540 nm., em. 590 nm.) were measured in a fluororescence plate reader.

In this assay, the inhibitory effect of different compound concentrations (range 10 μM to 0.1 nM) was determined and used to calculate an IC_{50} (M) and pIC_{50} (−log IC_{50}) value. As a counterscreen the same experiment was performed in the presence of 10 ng/ml murine IL3.

Ba/F3-KDR (Minus IL3 or Plus IL3) (Cellular Proliferation Assay)

In a 384 well plate, 100 nl of compound dilution in DMSO was sprayed before adding 50 μl cell culture medium (phenol red free RPMI-1640, 10% FBS, 2 mM L-Glutamine and 50 μg/ml Gentamycin) containing 20000 cells per well of Ba/F3-KDR-transfected cells. Cells were put in an incubator at 37° C. and 5% CO_2. After 24 hours, 10 μl of Alamar Blue solution (0.5 mM $K_3Fe(CN)_6$, 0.5 mM $K_4Fe(CN)_6$, 0.15 mM Resazurin and 100 mM Phosphate Buffer) was added to the wells, incubated for 4 hours at 37° C. and 5% CO_2 before RFU's (Relative Fluorescence Units) (ex. 540 nm., em. 590 nm.) were measured in a fluororescence plate reader.

In this assay, the inhibitory effect of different compound concentrations (range 10 μM to 0.1 nM) was determined and used to calculate an IC_{50} (M) and pIC_{50} (−log IC_{50}) value. As a counterscreen the same experiment was performed in the presence of 10 ng/ml murine IL3.

Ba/F3-Flt3 (Minus IL3 or Plus IL3) (Cellular Proliferation Assay)

In a 384 well plate, 100 nl of compound dilution in DMSO was sprayed before adding 50 µl cell culture medium (phenol red free RPMI-1640, 10% FBS, 2 mM L-Glutamine and 50 µg/ml Gentamycin) containing 20000 cells per well of Ba/F3-Flt3-transfected cells. Cells were put in an incubator at 37° C. and 5% CO_2. After 24 hours, 10 µl of Alamar Blue solution (0.5 mM $K_3Fe(CN)_6$, 0.5 mM $K_4Fe(CN)_6$, 0.15 mM Resazurin and 100 mM Phosphate Buffer) was added to the wells, incubated for 4 hours at 37° C. and 5% CO_2 before RFU's (Relative Fluorescence Units) (ex. 540 nm., em. 590 nm.) were measured in a fluororescence plate reader.

In this assay, the inhibitory effect of different compound concentrations (range 10 µM to 0.1 nM) was determined and used to calculate an IC_{50} (M) and pIC_{50} (−log IC_{50}) value. As a counterscreen the same experiment was performed in the presence of 10 ng/ml murine IL3.

Ba/F3-FGFR4 (Cellular Proliferation Assay)

In a 384 well plate, 100 n1 of compound dilution in DMSO was sprayed before adding 50 µl cell culture medium (phenol red free RPMI-1640, 10% FBS, 2 mM L-Glutamine and 50 µg/ml Gentamycin) containing 20000 cells per well of Ba/F3-FGFR4-transfected cells. Cells were put in an incubator at 37° C. and 5% CO2. After 24 hours, 10 µl of Alamar Blue solution (0.5 mM $K_3Fe(CN)_6$, 0.5 mM $K_4Fe(CN)_6$, 0.15 mM Resazurin and 100 mM Phosphate Buffer) was added to the wells, incubated for 4 hours at 37° C. and 5% CO_2 before RFU's (Relative Fluorescence Units) (ex. 540 nm., em. 590 nm.) were measured in a fluororescence plate reader.

In this assay, the inhibitory effect of different compound concentrations (range 10 µM to 0.1 nM) was determined and used to calculate an IC_{50} (M) and pIC_{50} (−log IC_{50}) value.

Data for the compounds of the invention in the above assays are provided in Table A2. (If data were generated multiple times for a compound or different batches were tested, average values are reported)

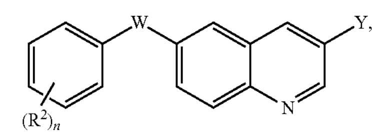
Comp. No.	FGFR 1 pIC50	FGFR 2 pIC50	hFGFR3 pIC50	FGFR 4 pIC50	VEGFR KDR pIC50	BAF3-FGFR1 (MIN IL3 pIC50)	BAF3-FGFR1 (PLUS IL3 pIC50)	BAF3-FGFR3 (MIN IL3 Alamar Blue-pIC50)	BAF3-FGFR3 (PLUS IL3 Alamar Blue pIC50)	BAF3-KDR (MIN IL3 Alamar Blue pIC50)	BAF3-KDR (PLUS IL3 Alamar Blue pIC50)	BAF3-FLT3 (MIN IL3 Alamar Blue pIC50)	BAF3-FLT3 (PLUS IL3 Alamar Blue pIC50)	BAF3-FGFR4 (pIC50)
1	8.455	8.305	8.1	7.86	7.13	7.4	<5	7.555	<5	5.635	<5	~5	<5	7.19
3	7.86	7.83	8.38	7.42	7.04	6.31	5.3	6.33	<5	5.65	<5	5.52	<5	6.11
4	7.72	7.87	8.23	7.51	6.86	6.26	5.15	6.17	<5	5.45	<5	5.35	<5	5.87
5	7.59	7.5	7.64	7.04	6.61	5.79	~5.04	5.67	<5	5.18	<5	5.06	<5	5.5
6	7.82	7.52	7.87	6.82	6.37	5.7	5.13	5.79	<5	5.07	<5	5.2	<5	5.4
16	8.03	7.81	7.87	7.43	6.05	>8	5.45	>8	<5	<5	<5	5.19	5.04	8.21
17	7.08	6.92	7.23	6.56	<6	7.35	5.09	7.63	<5	<5	<5	<5	<5	6.98
7	6.08	<6	6.04	<6	<6	<5	<5	<5	<5	<5	<5	<5	<5	<5
12	6.53	6.38	6.63	<6.03	<6	<5.03	<5	~5.075	<5	<5	<5	<5.47	<5.47	<5
8	8.11	7.7	7.49	6.93	6.09	6.27	<5	6.14	<5	<5	<5	<5.47	<5.47	5.64
9	8.25	8.11	7.96	6.84	6.78	6.14	<5	6.17	<5	<5	<5	<5	<5	5.18
10	7.46	7.89	7.81	7.08	7.09	6.03	<5	6.2	<5	5.11	<5	<5	<5	5.63
11	8.44	8.64	8.47	7.7	7.35	6.67	<5	6.97	<5	5.42	<5	<5	<5	6.39
Int. 8	7.02	7.43	7.43	6.31	6.5	5.29	<5	~5.53	<5	<5	<5	<5	<5	5.04
18	8.56	8.6	8.9	8.32	6.94	6.88	<5	7.22	<5	5.01	<5	<5	<5	6.57
27	8.785	8.25	8.625	8.505	7.425	8.715	5.16	8.22	<5	5.335	<5	<5	<5	8.18
19	7.96	7.94	8.25	7.22	7	6.32	<5	6.26	<5	5.1	<5	6.03	<5	5.71
24	8.73	8.31	~8.96	8.1	6.54	7.73	<5	~7.67	<5	5.05	<5	<5	<5	6.6
25	7.91	7.71	8.23	7.22	6.23	6.57	<5	6.76	<5	<5	<5	<5	<5	6.07
22	8.92	8.41	8.62	8.36	7.36	7.85	5.05	7.78	<5	5.79	<5	5.22	<5	~7.11
21	8.83	8.59	8.47	8.27	6.99	7.55	<5	7.57	<5	5.49	<5	5.09	<5	6.79
14	9.13	8.28	8.46	8.13	7.02	7.2	<5	~6.95	<5	5.45	<5	<5	<5	6.7
13	8.6	8.18	8.31	8.06	6.89	7.23	<5	7	<5	5.57	<5			6.81
2	8.88	8.49	8.41	8.4	7.59	8.3	5.09	7.86	<5	6.18	<5	5.34	<5	7.83
26	8.32	7.98	8.31	7.9	6.37	7.95	5.12	8.17	<5	5.11	<5	5.16	~5	7.77
47	8.93	8.41	8.88	8.66	7.93	~8.03	<5	8.46	<5	6.44	<5	5.14	<5	7.44
42	8.94	8.50	8.47	8.54	7.80	8.95	5.25	8.25	<5	6.95	<5	5.70	<5	8.25
48	8.08	7.84	8.10	7.50	6.54	7.24	5.13	7.62	<5	5.02	<5	5.23	<5	7.17
43	8.97	8.61	8.62	8.58	7.83	8.68	5.05	~8	<5	6.51	<5	5.24	<5	~8.02
44	8.24	8.49	8.77	~7.87	7.28	5.65	<5	6.61	<5	5.18	<5	—	—	6.00
48a	6.53	6.77	6.38	6.08	<6	<5	<5	<5	<5	<5	<5	—	—	<5
46	8.20	8.44	8.61	7.77	5.99	5.89	<5	5.68	<5	<5	<5	—	—	5.28
50	7.16	7.26	7.24	6.59	<6	5.11	<5	5.19	<5	<5	<5	—	—	<5
51	8.56	8.40	8.10	7.86	6.77	6.13	<5	5.82	<5	5.15	~5.22	—	—	5.87
52	7.80	8.18	8.07	7.78	6.03	5.77	<5	6.00	<5	<5	<5	—	—	5.48
54	6.42	6.74	6.84	<6	<6	<5	<5	5.16	<5	<5	<5	—	—	<5
55	7.04	7.7	7.69	6.88	<6	5.64	<5	5.77	<5	<5	<5	—	—	5.37
57	8.55	8.64	8.98	8.35	6.34	6.75	<5	~6.77	<5	<5	<5	<5	<5	6.16
58	8.03	7.89	7.56	6.73	6.14	~5.86	<5	5.57	<5	<5	<5	<5	<5	<5
59	8.33	8.52	8.76	8.13	6.07	6.36	<5	6.50	<5	<5	<5	<5	<5	6.02
60	7.94	7.71	7.50	6.60	<6	5.37	<5	5.22	<5	<5	<5	<5	<5	<5
31	7.66	7.51	7.73	6.59	6.8	5.65	<5	5.46	<5	<5	<5	—	—	5.12
62	8.53	8.68	8.84	8.48	6.59	6.63	<5	6.75	<5	<5	<5			6.24
61	7.85	~7.90	8.57	7.68	6.72	6.02	~5.02	5.84	<5	5.40	<5			5.66
30	7.67	7.46	7.66	6.52	6.48	6.03	5.16	5.89	5.18	5.55	<5			5.25
41	7.63	7.69	7.41	6.78	<6	6.43	<5	6.30	<5	<5	<5			5.78
29	7.27	~7.17	7.34		6.25	5.45	<5	5.29	<5	5.15	<5			<5

-continued

Comp. No.	FGFR 1 pIC50	FGFR 2 pIC50	hFGFR3 pIC50	FGFR 4 pIC50	VEGFR KDR pIC50	BAF3-FGFR1 (MIN IL3 pIC50)	BAF3-FGFR1 (PLUS IL3 pIC50)	BAF3-FGFR3 (MIN IL3 Alamar Blue-pIC50)	BAF3-FGFR3 (PLUS IL3 Alamar Blue pIC50)	BAF3-KDR (MIN IL3 Alamar Blue pIC50)	BAF3-KDR (PLUS IL3 Alamar Blue pIC50)	BAF3-FLT3 (MIN IL3 Alamar Blue pIC50)	BAF3-FLT3 (PLUS IL3 Alamar Blue pIC50)	BAF3-FGFR4 (pIC50)
39	6.77	6.55	6.75	<6	<6	5.09	<5	<5	<5	<5	<5			<5
40	6.73	6.52	6.66		<6	<5	<5	5.08	<5	<5	<5			<5
34	6.71	6.73	7.67	6.38	<6	5.01	<5	5.16	<5	<5	<5			<5
36	<6	<6	<6	<6	<6									

The invention claimed is:

1. A compound selected from the group consisting of a compound of formula (I):



(I)

a tautomeric form and stereochemically isomeric form thereof, wherein W is —N(R^3)— or —C($R^{3a}R^{3b}$)—;

each R^2 is independently selected from hydroxyl, halogen, cyano, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkoxy, hydroxyC_{1-4}alkyl, hydroxyC_{1-4}alkoxy, haloC_{1-4}alkyl, haloC_{1-4}alkoxy, hydroxyhaloC_{1-4}alkyl, hydroxyhaloC_{1-4}alkoxy, C_{1-4}alkoxyC_{1-4}alkyl, halo-C_{1-4}alkoxyC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl wherein each C_{1-4}alkyl may optionally be substituted with one or two hydroxyl groups, hydroxyhaloC_{1-4}alkoxy-C_{1-4}alkyl, C_{1-4}alkyl substituted with —NR^7R^8, C_{1-4}alkyl substituted with —C(═O)—NR^7R^8, C_{1-4}alkoxy substituted with —NR^7R^8, C_{1-4}alkoxy substituted with —C(═O)—NR^7R^8, —$NR^7R^8$and —C(═O)—NR^7R^8;

Y represents -E-D;

D represents a 3, 4, 5, 6, 7 or 8 membered monocyclic carbocyclyl or a 3, 4, 5, 6, 7 or 8 membered monocyclic heterocyclyl containing at least one heteroatom selected from N, O and S, wherein said carbocyclyl and heterocyclyl may each be optionally substituted by one or more R^1 groups;

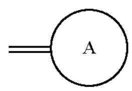
E represents a bond;

R^1 represents hydrogen, halo, cyano, C_{1-6}alkyl, C_{1-6}alkoxy, —C(═O)—O— C_{1-6}alkyl, C_{2-4}alkenyl, hydroxyC_{1-6}alkyl, haloC_{1-6}alkyl, hydroxyhalo-C_{1-6}alkyl, cyanoC_{1-4}alkyl, C_{1-6}alkoxyC_{1-6}alkyl wherein each C_{1-6}alkyl may optionally be substituted with one or two hydroxyl groups, —NR^4R^5, C_{1-6}alkyl substituted with —O—C(═O)— C_{1-6}alkyl, C_{1-6}alkyl substituted with —NR^4R^5, —C(═O)—NR^4R^5, —C(═O)—C_{1-6}alkyl-NR^4R^5, C_{1-6}alkyl substituted with —C(═O)—NR^4R^5, —S(═O)$_2$—C_{1-6}alkyl, —S(═O)$_2$-haloC_{1-6}alkyl, —S(═O)$_2$—$NR^{14}R^{15}$, C_{1-6}alkyl substituted with —S(═O)$_2$—C_{1-6}alkyl, C_{1-6}alkyl substituted with —S(═O)$_2$-haloC_{1-6}alkyl, C_{1-6}alkyl substituted with —S(═O)$_2$—$NR^{14}R^{15}$, C_{1-6}alkyl substituted with —NH—S(═O)$_2$—C_{1-6}alkyl, C_{1-6}alkyl substituted with —NH—S(═O)$_2$-haloC_{1-6}alkyl, C_{1-6}alkyl substituted with —NR^{12}—S(═O)$_2$—$NR^{14}R^{15}$, R^6, C_{1-6}alkyl substituted with R^6, —C(═O)—R^6, C_{1-6}alkyl substituted with —C(═O)—R^6, hydroxyC_{1-6}alkyl substituted with R^6, C_{1-6}alkyl substituted with —Si(CH_3)$_3$, C_{1-6}alkyl substituted with —P(═O)(OH)$_2$ or C_{1-6}alkyl substituted with —P(═O)(OC_{1-6}alkyl)$_2$;

R^{3a} represents —$NR^{10}R^{11}$, hydroxyl, C_{1-6}alkoxy, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxy substituted with —$NR^{10}R^{11}$, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, haloC_{1-6}alkyl optionally substituted with —O—C(═O)—C_{1-6}alkyl, hydroxyC_{1-6}alkyl optionally substituted with —O—C(═O)—C_{1-6}alkyl, hydroxyC_{2-6}alkenyl, hydroxyC_{2-6}alkynyl, hydroxyhaloC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkyl substituted with carboxyl, C_{1-6}alkyl substituted with —C(═O)—C_{1-6}alkyl, C_{1-6}alkyl substituted with —C(═O)—O—C_{1-6}alkyl, C_{1-6}alkyl substituted with C_{1-6}alkoxyC_{1-6}alkyl-O—C(═O)—, C_{1-6}alkyl substituted with C_{1-6}alkoxy-C_{1-6}alkyl-C(═O)—, C_{1-6}alkyl substituted with —O—C(═O)—C_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkyl wherein each C_{1-6}alkyl may optionally be substituted with one or two hydroxyl groups or with —O—C(═O)—C_{1-6}alkyl, C_{2-6}alkenyl substituted with C_{1-6}alkoxy, C_{2-6}alkynyl substituted with C_{1-6}alkoxy, C_{1-6}alkyl substituted with R^9 and optionally substituted with —O—C(═O)—C_{1-6}alkyl, C_{1-6}alkyl substituted with —C(═O)—R^9, C_{1-6}alkyl substituted with hydroxyl and R^9, C_{2-6}alkenyl substituted with R^9, C_{2-6}alkynyl substituted with R^9, C_{1-6}alkyl substituted with —$NR^{10}R^{11}$, C_{2-6}alkenyl substituted with —$NR^{10}R^{11}$, C_{2-6}alkynyl substituted with —$NR^{10}R^{11}$, C_{1-6}alkyl substituted with hydroxyl and —$NR^{10}R^{11}$, C_{1-6}alkyl substituted with one or two halogens and —$NR^{10}R^{11}$, —C_{1-6}alkyl-C(R^{12})═N—O—R^{12}, C_{1-6}alkyl substituted with —C(═O)—$NR^{10}R^{11}$, C_{1-6}alkyl substituted with —O—C(═O)—$NR^{10}R^{11}$, —S(═O)$_2$—C_{1-6}alkyl, —S(═O)$_2$-haloC_{1-6}alkyl, —S(═O)$_2$—$NR^{14}R^{15}$, C_{1-6}alkyl substituted with —S(═O)$_2$—C_{1-6}alkyl, C_{1-6}alkyl substituted with —S(═O)$_2$-haloC_{1-6}alkyl, C_{1-6}alkyl substituted with —S(═O)$_2$—$NR^{14}R^{15}$, C_{1-6}alkyl substituted with —NR^{12}—S(═O)$_2$—C_{1-6}alkyl, C_{1-6}alkyl substituted with —NH—S(═O)$_2$-haloC_{1-6}alkyl, C_{1-6}alkyl substituted with —NR^{12}—S(═O)$_2$—$NR^{14}R^{15}$, R^{13}, C_{1-6}alkyl substituted with —P(═O)(OH)$_2$ or C_{1-6}alkyl substituted with —P(═O)(OC_{1-6}alkyl)$_2$;

R^{3b} represents hydrogen or hydroxyl; provided that if R^{3a} represents —$NR^{10}R^{11}$, then R^{3b} represents hydrogen; or

R^{3a} and R^{3b} are taken together to form ═O, to form ═NR^{10}, to form cyclopropyl together with the carbon atom to which they are attached, to form ═CH—C_{0-4}alkyl substituted with R^{3c}, or to form



wherein ring A is a monocyclic 5 to 7 membered saturated heterocycle containing one heteroatom selected from N, O and S, said heteroatom not being positioned in alpha position of the double bond, wherein ring A is optionally being substituted with cyano, C_{1-4}alkyl, hydroxyC_{1-4}alkyl, H_2N—C_{1-4}alkyl, (C_{1-4}alkyl)NH—C_{1-4}alkyl, (C_{1-4}alkyl)$_2$N—C_{1-4}alkyl, haloC_{1-4}alkyl) NH—C_{1-4}alkyl, C_{1-4}alkoxy-C_{1-4}alkyl, —C(═O)—NH_2, —C(═O)—NH(C_{1-4}alkyl), —C(═O)—N(C_{1-4}alkyl)$_2$;

R^{3c} represents hydrogen, hydroxyl, C_{1-6}alkoxy, R^9, —$NR^{10}R^{11}$, cyano, —C(═O)—C_{1-6}alkyl or —CH(OH)—C_{1-6}alkyl;

R^3 represents hydroxyl, C_{1-6}alkoxy, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxy substituted with —$NR^{10}R^{11}$, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, haloC_{1-6}alkyl optionally substituted with —O—C(═O)—C_{1-6}alkyl, hydroxy-C_{1-6}alkyl optionally substituted with —O—C(═O)—C_{1-6}alkyl, hydroxyC_{2-6}alkenyl, hydroxyC_{2-6}alkynyl, hydroxyhaloC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkyl substituted with carboxyl, C_{1-6}alkyl substituted with —C(═O)—C_{1-6}alkyl, C_{1-6}alkyl substituted with —C(═O)—O—C_{1-6}alkyl, C_{1-6}alkyl substituted with C_{1-6}alkoxyC_{1-6}alkyl-O—C(═O)—, C_{1-6}alkyl substituted with C_{1-6}alkoxyC_{1-6}alkyl-C(═O)—, C_{1-6}alkyl substituted with —O—C(═O)—C_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkyl wherein each C_{1-6}alkyl may optionally be substituted with one or two hydroxyl groups or with —O—C(═O)—C_{1-6}alkyl, C_{2-6}alkenyl substituted with C_{1-6}alkoxy, C_{2-6}alkynyl substituted with C_{1-6}alkoxy, C_{1-6}alkyl substituted with R^9 and optionally substituted with —O—C(═O)—C_{1-6}alkyl, C_{1-6}alkyl substituted with —C(═O)—R^9, C_{1-6}alkyl substituted with hydroxyl and R^9, C_{2-6}alkenyl substituted with R^9, C_{2-6}alkynyl substituted with R^9, C_{1-6}alkyl substituted with —$NR^{10}R^{11}$, C_{2-6}alkenyl substituted with —$NR^{10}R^{11}$, C_{2-6}alkynyl substituted with —$NR^{10}R^{11}$, C_{1-6}alkyl substituted with hydroxyl and —$NR^{10}R^{11}$, C_{1-6}alkyl substituted with one or two halogens and —$NR^{10}R^{11}$, —C_{1-6}alkyl-C(R^{12})═N—O—R^{12}, C_{1-6}alkyl substituted with —C(═O)—$NR^{10}R^{11}$, C_{1-6}alkyl substituted with —O—C(═O)—$NR^{10}R^{11}$, —S(═O)$_2$—C_{1-6}alkyl, —S(═O)$_2$-halo-C_{1-6}alkyl, —S(═O)$_2$—$NR^{14}R^{15}$, C_{1-6}alkyl substituted with —S(═O)$_2$—C_{1-6}alkyl, C_{1-6}alkyl substituted with —S(═O)$_2$-haloC_{1-6}alkyl, C_{1-6}alkyl substituted with —S(═O)$_2$—$NR^{14}R^{15}$, C_{1-6}alkyl substituted with —NR^{12}—S(═O)$_2$—C_{1-6}alkyl, C_{1-6}alkyl substituted with —NH—S(═O)$_2$-haloC_{1-6}alkyl, C_{1-6}alkyl substituted with —NR^{12}—S(═O)$_2$—$NR^{14}R^{15}$, R^{13}, C_{1-6}alkyl substituted with —P(═O)(OH)$_2$ or C_{1-6}alkyl substituted with —P(═O)(OC_{1-6}alkyl)$_2$;

R^4 and R^5 each independently represent hydrogen, C_{1-6}alkyl, C_{1-6}alkyl substituted with —$NR^{14}R^{15}$ hydroxyC_{1-6}alkyl, haloC_{1-6}alkyl, hydroxyhalo-C_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkyl wherein each C_{1-6}alkyl may optionally be substituted with one or two hydroxyl groups, —S(═O)$_2$—C_{1-6}alkyl, —S(═O)$_2$-halo-C_{1-6}alkyl, —S(═O)$_2$—$NR^{14}R^{15}$, —C(═O)—$NR^{14}R^{15}$, —C(═O)—O—C_{1-6}alkyl, —C(═O)—R^{13}, C_{1-6}alkyl substituted with —S(═O)$_2$—C_{1-6}alkyl, C_{1-6}alkyl substituted with —S(═O)$_2$-haloC_{1-6}alkyl, C_{1-6}alkyl substituted with —S(═O)$_2$—$NR^{14}R^{15}$, C_{1-6}alkyl substituted with —NH—S(═O)$_2$—C_{1-6}alkyl, C_{1-6}alkyl substituted with —NH—S(═O)$_2$-haloC_{1-6}alkyl, C_{1-6}alkyl substituted with —NH—S(═O)$_2$—$NR^{14}R^{15}$, R^{13} or C_{1-6}alkyl substituted with R^{13};

R^6 represents C_{3-8}cycloalkyl, C_{3-8}cycloalkenyl, phenyl, 4 to 7-membered monocyclic heterocyclyl containing at least one heteroatom selected from N, O and S; said C_{3-8}cycloalkyl, C_{3-8}cycloalkenyl, phenyl, 4 to 7-membered monocyclic heterocyclyl, optionally and each independently being substituted by 1, 2, 3, 4 or 5 substituents, each substituent independently being selected from cyano, C_{1-6}alkyl, cyanoC_{1-6}alkyl, hydroxyl, carboxyl, hydroxyC_{1-6}alkyl, halogen, haloC_{1-6}alkyl, hydroxyhaloC_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkyl-O—C(═O)—, —$NR^{14}R^{15}$, —C(═O)—$NR^{14}R^{15}$, C_{1-6}alkyl substituted with —$NR^{14}R^{15}$, C_{1-6}alkyl substituted with —C(═O)—$NR^{14}R^{15}$, —S(═O)$_2$—C_{1-6}alkyl, —S(═O)$_2$-haloC_{1-6}alkyl, —S(═O)$_2$—$NR^{14}R^{15}$, C_{1-6}alkyl substituted with —S(═O)$_2$—C_{1-6}alkyl, C_{1-6}alkyl substituted with —S(═O)$_2$-haloC_{1-6}alkyl, C_{1-6}alkyl substituted with —S(═O)$_2$—$NR^{14}R^{15}$, C_{1-6}alkyl substituted with —NH—S(═O)$_2$—C_{1-6}alkyl, C_{1-6}alkyl substituted with —NH—S(═O)$_2$-haloC_{1-6}alkyl and C_{1-6}alkyl substituted with —NH—S(═O)$_2$—$NR^{14}R^{15}$;

R^7 and R^8 each independently represent hydrogen, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, haloC_{1-6}alkyl, hydroxy-haloC_{1-6}alkyl or C_{1-6}alkoxyC_{1-6}alkyl;

R^9 represents C_{3-8}cycloalkyl, C_{3-8}cycloalkenyl, phenyl, or 3, 4, 5, 6, 7 or 8 membered monocyclic heterocyclyl containing at least one heteroatom selected from N, O and S, said C_{3-8}cycloalkyl, C_{3-8}cycloalkenyl, phenyl, or 3, 4, 5, 6, 7 or 8 membered monocyclic heterocyclyl each optionally and each independently being substituted with 1, 2, 3, 4 or 5 substituents, each substituent independently being selected from ═O, C_{1-4}alkyl, hydroxyl, carboxyl, hydroxyC_{1-4}alkyl, cyano, cyanoC_{1-4}alkyl, C_{1-4}alkyl-O—C(═O)—, C_{1-4}alkyl substituted with C_{1-4}alkyl-O—C(═O)—C_{1-4}alkyl-C(═O)—, C_{1-4}alkoxyC_{1-4}alkyl wherein each C_{1-4}alkyl may optionally be substituted with one or two hydroxyl groups, halogen, haloC_{1-4}alkyl, hydroxyhaloC_{1-4}alkyl, —$NR^{14}R^{15}$, —C(═O)—$NR^{14}R^{15}$, C_{1-4}alkyl substituted with —$NR^{14}R^{15}$, C_{1-4}alkyl substituted with —C(═O)—$NR^{14}R^{15}$, C_{1-4}alkoxy, —S(═O)$_2$—C_{1-4}alkyl, —S(═O)$_2$-haloC_{1-4}alkyl, —S(═O)$_2$—$NR^{14}R^{15}$, C_{1-4}alkyl substituted with —S(═O)$_2$—$NR^{14}R^{15}$, C_{1-4}alkyl substituted with —NH—S(═O)$_2$—C_{1-4}alkyl, C_{1-4}alkyl substituted with —NH—S(═O)$_2$-haloC_{1-4}alkyl, C_{1-4}alkyl substituted with —NH—S(═O)$_2$—$NR^{14}R^{15}$, R^{13}, —C(═O)—R^{13}, C_{1-4}alkyl substituted with R^{13}, phenyl optionally substituted with R^{16}, phenylC_{1-6}alkyl wherein the phenyl is optionally substituted with R^{16}, a 5 or 6-membered aromatic monocyclic heterocyclyl containing at least one heteroatom selected from N, O and S wherein said heterocyclyl is optionally substituted with R^{16};

R^{10} and R^{11} each independently represent hydrogen, carboxyl, C_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkyl substituted with —$NR^{14}R^{15}$, C_{1-6}alkyl substituted with —C(═O)—$NR^{14}R^{15}$, haloC_{1-6}alkyl, hydroxy-C_{1-6}alkyl, hydroxyhaloC_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl wherein each C_{1-6}alkyl may optionally be substituted with one or two hydroxyl groups, R^6, C_{1-6}alkyl substituted with R^6, —C(═O)—

R^6, —C(=O)—C_{1-6}alkyl, —C(=O)-hydroxy-C_{1-6}alkyl, —C(=O)-haloC_{1-6}alkyl, —C(=O)-hydroxyhaloC_{1-6}alkyl, C_{1-6}alkyl substituted with —Si$(CH_3)_3$, —S(=O)$_2$—C_{1-6}alkyl, —S(=O)$_2$-halo-C_{1-6}alkyl, —S(=O)$_2$—$NR^{14}R^{15}$, C_{1-6}alkyl substituted with —S(=O)$_2$—C_{1-6}alkyl, C_{1-6}alkyl substituted with —S(=O)$_2$-haloC_{1-6}alkyl, C_{1-6}alkyl substituted with —S(=O)$_2$—$NR^{14}R^{15}$, C_{1-6}alkyl substituted with —NH—S(=O)$_2$—C_{1-6}alkyl, C_{1-6}alkyl substituted with —NH—S(=O)$_2$-haloC_{1-6}alkyl, C_{1-6}alkyl substituted with carboxyl, or C_{1-6}alkyl substituted with —NH—S(=O)$_2$—$NR^{14}R^{15}$;

R^{12} represents hydrogen or C_{1-4}alkyl optionally substituted with C_{1-4}alkoxy;

R^{13} represents C_{3-8}cycloalkyl or a saturated 4 to 6-membered monocyclic heterocyclyl containing at least one heteroatom selected from N, O and S, wherein said C_{3-8}cycloalkyl or monocyclic heterocyclyl is optionally substituted with 1, 2 or 3 substituents each independently selected from halogen, hydroxyl, C_{1-6}alkyl, haloC_{1-6}alkyl, =O, cyano, —C(=O)—C_{1-6}alkyl, C_{1-6}alkoxy, and —$NR^{14}R^{15}$;

R^{14} and R^{15} each independently represent hydrogen, or haloC_{1-4}alkyl, or C_{1-4}alkyl optionally substituted with a substituent selected from hydroxyl, C_{1-4}alkoxy, amino and mono- or di(C_{1-4}alkyl)amino;

R^{16} represents hydroxyl, halogen, cyano, C_{1-4}alkyl, C_{1-4}alkoxy, —$NR^{14}R^{15}$ or —C(=O)$NR^{14}R^{15}$; and

n independently represents an integer equal to 0, 1, 2, 3 or 4;

or an N-oxide thereof, a pharmaceutically acceptable salt thereof or a solvate thereof.

2. A compound according to claim **1** wherein D is:

(i) optionally substituted pyrazolyl; or

(ii) piperidinyl, pyridinyl, phenyl, pyrolyl, imidazolyl, triazolyl, thiazolyl, cyclopentyl, azetidinyl, morpholinyl, tetrazolyl, oxazolyl, piperazinyl, 1,2,3,6-tetrahydropyridinyl, 2,5-dihydropyrolyl, pyrimidinyl, pyrolidinyl, said rings being optionally substituted,

or an N-oxide thereof, a pharmaceutically acceptable salt thereof or a solvate thereof.

3. A compound according to claim **1** wherein W is —N(R^3)—,

or an N-oxide thereof, a pharmaceutically acceptable salt thereof or a solvate thereof.

4. A compound according to claim **1** wherein W is —C($R^{3a}R^{3b}$)—,

or an N-oxide thereof, a pharmaceutically acceptable salt thereof or a solvate thereof.

5. A compound according to claim **1** wherein R^1 represents C_{1-6}alkyl,

or an N-oxide thereof, a pharmaceutically acceptable salt thereof or a solvate thereof.

6. A compound according to claim **1** wherein R^2:

(i) is independently selected from hydroxyl, halogen, cyano, C_{1-4}alkyl, C_{2-4}alkenyl, C_{1-4}alkoxy, hydroxyC_{1-4}alkyl, hydroxyC_{1-4}alkoxy, haloC_{1-4}alkoxy, C_{1-4}alkoxyC_{1-4}alkyl, C_{1-4}alkyl substituted with NR^7R^8, C_{1-4}alkoxy substituted with NR^7R^8, —$NR^7R^8$and —C(=O)—NR^7R^8; or

(ii) represents C_{1-4}alkoxy; or

(iii) represents C_{1-4}alkoxy or halogen,

or an N-oxide thereof, a pharmaceutically acceptable salt thereof or a solvate thereof.

7. A compound according to claim **1** wherein R^3 represents:

(i) C_{1-6}alkyl, hydroxyC_{1-6}alkyl, hydroxyhaloC_{1-6}alkyl, haloC_{1-6}alkyl, C_{1-6}alkyl substituted with —C(=O)—C_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkyl wherein each C_{1-6}alkyl may optionally be substituted with one or two hydroxyl groups, C_{1-6}alkyl substituted with R^9, C_{1-6}alkyl substituted with —$NR^{10}R^{11}$, C_{1-6}alkyl substituted with hydroxyl and —$NR^{10}R^{11}$, C_{1-6}alkyl substituted with one or two halogens and —$NR^{10}R^{11}$, C_{1-6}alkyl substituted with —C(=O)—O—C_{1-6}alkyl, C_{1-6}alkyl substituted with —O—C(=O)—$NR^{10}R^{11}$, C_{1-6}alkyl substituted with carboxyl, C_{1-6}alkyl substituted with —NR^{12}—S(=O)$_2$—C_{1-6}alkyl, C_{1-6}alkyl substituted with —NR^{12}—S(=O)$_2$—$NR^{14}R^{15}$, C_{1-6}alkyl substituted with hydroxyl and R^9, —C_{1-6}alkyl-C(R^{12})=N—O—R^{12}, C_{1-6}alkyl substituted with —C(=O)—$NR^{10}R^{11}$, C_{1-6}alkyl substituted with —C(=O)—R^9, C_{2-6}alkynyl substituted with R^9, hydroxyC_{1-6}alkoxy, C_{2-6}alkenyl, C_{2-6}alkynyl or R^{13}; or

(ii) hydroxyC_{1-6}alkyl, hydroxyhaloC_{1-6}alkyl, C_{1-6}alkyl substituted with R^9, C_{1-6}alkyl substituted with —$NR^{10}R^{11}$, C_{2-6}alkynyl substituted with R^9, or C_{2-6}alkynyl,

or an N-oxide thereof, a pharmaceutically acceptable salt thereof or a solvate thereof.

8. A compound according to claim **1** wherein R^{3a} represents hydroxyl, C_{1-6}alkyl substituted with —C(=O)—$NR^{10}R^{11}$, cyanoC_{1-6}alkyl, hydroxyC_{1-6}alkyl, C_{1-6}alkyl substituted with —C(=O)—O—C_{1-6}alkyl,

or an N-oxide thereof, a pharmaceutically acceptable salt thereof or a solvate thereof.

9. A compound according to claim **1** wherein R^{3b} represents hydrogen,

or an N-oxide thereof, a pharmaceutically acceptable salt thereof or a solvate thereof.

10. A compound according to claim **1** wherein:

(i) n represents an integer equal to 2, 3 or 4; R^2 represents C_{1-4}alkoxy or halo; R^3 represents hydroxyC_{1-6}alkyl, hydroxyhaloC_{1-6}alkyl, C_{1-6}alkyl substituted with R^9, C_{1-6}alkyl substituted with —$NR^{10}R^{11}$, C_{2-6}alkynyl substituted with R^9, or C_{2-6}alkynyl; D represents pyrazolyl, optionally substituted with C_{1-6}alkyl, hydroxyC_{1-6}alkyl or R^6; W is —N(R^3)— or —C($R^{3a}R^{3b}$)— wherein R^{3a} is hydroxyl, R^{3b} is hydrogen; or

(ii) n represents an integer equal to 2, 3 or 4; R^2 represents C_{1-4}alkoxy or halogen; R^3 represents hydroxyC_{1-6}alkyl, hydroxyhaloC_{1-6}alkyl, C_{1-6}alkyl substituted with R^9, C_{1-6}alkyl substituted with —$NR^{10}R^{11}$, C_{2-6}alkynyl substituted with R^9 or C_{2-6}alkynyl; R^{3a} represents hydroxyl, C_{1-6}alkyl substituted with —C(=O)—$NR^{10}R^{11}$, cyanoC_{1-6}alkyl, hydroxyC_{1-6}alkyl, C_{1-6}alkyl substituted with —C(=O)—O—C_{1-6}alkyl; R^{3b} represents hydrogen; or R^{3a} and R^{3b} are taken together to form =O or to form =CH—C_{0-4}alkyl substituted with R^3C; D represents an optionally substituted 5 membered heterocycle, an optionally substituted 6 membered heterocycle or phenyl, or an N-oxide thereof, a pharmaceutically acceptable salt thereof or a solvate thereof.

11. A compound according to claim **1** or a pharmaceutically acceptable salt or solvate thereof.

12. A pharmaceutical composition comprising a compound according to claim **1**, or an N-oxide thereof, a pharmaceutically acceptable salt thereof or a solvate thereof.

13. A method for inhibiting a fibroblast growth factor receptor kinase, which method comprises contacting the kinase with a compound according to claim **1**, or an N-oxide thereof, a pharmaceutically acceptable salt thereof or a solvate thereof.

14. A method for inhibiting fibroblast growth factor receptor kinase activity in a subject, which method comprises administering to a subject in need thereof a compound according to claim **1**, or an N-oxide thereof, a pharmaceutically acceptable salt thereof or a solvate thereof.

15. A combination of a compound according to claim **1**, or an N-oxide thereof, a pharmaceutically acceptable salt thereof or a solvate thereof, with one or more anticancer agents.

16. A combination according to claim **15**, wherein the one or more anticancer agents comprises a kinase inhibitor.

17. A product containing as first active ingredient a compound according to claim **1**, or an N-oxide thereof, a pharmaceutically acceptable salt thereof or a solvate thereof, and as further active ingredient one or more anticancer agents, as a combined preparation for simultaneous, separate or sequential use in the treatment of patients suffering from cancer.

18. A product according to claim **17** wherein the one or more anticancer agents comprises a kinase inhibitor.

19. A compound according to claim **10** wherein n represents an integer equal to 2, 3 or 4; R^2 represents C_{1-4}alkoxy or halogen; R^3 represents hydroxyC_{1-6}alkyl, hydroxyhaloC_{1-6}alkyl, C_{1-6}alkyl substituted with R^9, C_{1-6}alkyl substituted with —$NR^{10}R^{11}$, C_{2-6}alkynyl substituted with R^9 or C_{2-6}alkynyl; R^{3a} represents hydroxyl, C_{1-6}alkyl substituted with —C(═O)—$NR^{10}R^{11}$, cyanoC_{1-6}alkyl, hydroxyC_{1-6}alkyl, C_{1-6}alkyl substituted with —C(═O)—O—C_{1-6}alkyl; R^{3b} represents hydrogen; or R^{3a} and R^{3b} are taken together to form ═O or to form ═CH—C_{0-4}alkyl substituted with R^3C; D represents an optionally substituted aromatic 5 membered heterocycle, an optionally substituted saturated, partially saturated or aromatic 6 membered heterocycle, or phenyl.

20. A compound according to claim **19** wherein D represents pyrazol-4-yl, optionally substituted with C_{1-6}alkyl, hydroxyC_{1-6}alkyl, C_{1-6}alkyl substituted with —S(═O)$_2$—C_{1-6}alkyl or R^6, or phenyl, or pyridyl or morpholinyl or 1,2,3,6-tetrahydropyridyl or pyrrolyl optionally substituted with C_{1-6}alkyl.

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